ISSN 1473-9348 Volume 8 Issue 5 November/December 2008

ACNR

www.acnr.co.uk

Advances in Clinical Neuroscience & Rehabilitation

Same... yet different

Up to 16 weeks between injections and ready-to-use[1]

NeuroBloc®

Botulinum Toxin Type B Injectable Solution 5,000U/mL

Adds efficiency to efficacy. That's smart.

ABBREVIATED PRESCRIBING INFORMATION

NeuroBloc® (Botulinum toxin Type B)

Please refer to the SPC before prescribing.

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

Indication: Treatment of cervical dystonia (torticollis).

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

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

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

Children and adolescents under 18 years: Not recommended

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

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

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

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

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

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

Shelf-life: 3 years. Chemical and physical in use stability has been demonstrated for up to 8 hours at 25°C

Special precautions for storage: 2°C – 8°C. Do not freeze. Protect from light. For storage conditions of the diluted medicinal product, see SPC

Legal Category: POM

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

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

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

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

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

Date of preparation: March 2008

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

References: 1. NeuroBloc Summary of Product Characteristics.

Eisai

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

under license from SOLSTICE NEUROSCIENCES

Lyme disease of the central nervous system is relatively rare, although not uncommonly considered in the differential diagnosis of patients with an array of neurological problems including facial palsies and a radiculitis. In this clear article by Unn Ljøstad and Åse Mygland, we are taken through the common clinical features of this condition and how it can be diagnosed. This article contains a couple of really useful tables summarising the main points, which overall makes for an extremely succinct, up to date account, of this condition.

Jone Furland Owe and Nils Erik Gilhus discuss an unusual aspect of myasthenia gravis – namely how it affects the heart. They conclude that "There is good evidence for myocardial pathology in MG patients, including a diversity of heart-reactive autoantibodies and focal inflammation with cellular infiltrates and myocardial necrosis. On the other hand, any firm clinical correlates to these findings have yet to be established". Interesting.

On the theme of epilepsy, Paul Johns and Maria Thom discuss in our neuropathology article the relationship between hippocampal sclerosis (HS) and epilepsy. It is well known that the two are associated but it is not clear whether one causes the other. In this article, the competing theories are discussed in particular whether seizures, especially early in life, cause HS or whether HS is consequent to a developmental problem which then causes seizures.

Plaha and colleagues in their article for the Neurosurgery series consider chronic subdural haematoma. They begin by discussing how such lesions come about and how the patient may present, before considering how to optimally treat it. An issue that is far from clearcut! This is an easy to read account which represents a measured and pragmatic approach to this relatively common neurological problem.

Michael Turner reports on the guidelines and stipulations for jockeys engaged in different types of horse racing and the consequences to them of a fall and a head injury. This is not an uncommon event as there are approximately 110,00 rides a year and "Amateur jockeys fall every 7.9 rides, Jump jockeys fall every 15.8 rides and Flat jockeys fall every 200-250 rides. It is therefore not surprising that horse racing has some of the highest rates of injury seen in any sport, including the highest rates of concussion and fatal accidents in the published literature. Concussion rates are in fact six times greater than in Australian Rules Football – the sport with the closest incidence of concussion." I think I will continue to walk and ride my bike.

In the first of our new series on Neuroradiology edited by Justin Cross we are treated to a sumptuously illustrated account on CT. In this first article by Justin we are introduced to the Compston effect and Hounsfield Units as well as having partial volume effects explained. This is a wonderful article that gives just the right amount of background physics and technical detail whilst also illustrating the role and value of this imaging modality to neurological practice in 2008.

In our Neurology and Literature series, Dr Pearce takes us through the Charles Bonnet syndrome and how it came to be called this and what exactly is meant by it. This article with a liberal sprinkling of original quotations from Dr Bonnet follows on from the earlier article we featured by Dominic Ffytche in *ACNR* 4.2 on visual hallucinations and optical illusions.

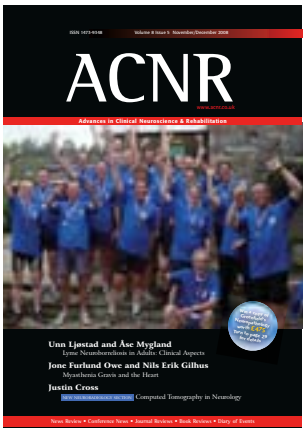
Heather Angus-Leppan gives us a picture of where the ABN is going (as opposed to where it has come from (see *ACNR* 7.5).We are also pleased to announce that Heather will be joining the editorial team of *ACNR*, helping to keep us abreast of developments within the ABN. Finally we have all our usual journal, conference and book reviews. Do enjoy and if you would like to become a part of the reviewing team just let us know by email to Rachael@acnr.co.uk.

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

Sadly we report that Dr Raymond D Adams passed away on the 18th October, aged 97. He made a colossal contribution to neurology. We were fortunate enough to be the recipient of some of that knowledge in the article he wrote for *ACNR* in issue 6:5 (Nov/Dec 2006).

ACNR is published by Whitehouse Publishing, 1 The Lynch, Mere, Wiltshire, BA12 6DQ.
Publisher: Rachael Hansford • **E.** rachael@acnr.co.uk

Advertising: Rachael Hansford, **T.** 01747 860168, **M.** 07989 470278, **E.** rachael@acnr.co.uk
Course Advertising: Nathalie Fricker, **E.** events@acnr.co.uk
Editorial: Anna Phelps, **E.** editorial@acnr.co.uk
Design & Production E. design.dept@sky.com
Printed by: Warners Midlands PLC, T. 01778 391000



Cover picture shows participants in the first ever ABN Triathlon, held at the Autumn meeting of the ABN in Aviemore recently. For a full report see page 35.

Contents

November/December 2008

As soon as first line oral dopamine agonists start to fail

Go directly to APO-go

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

For responsive patients with Early Complex PD, **APO-go** CDS is a highly effective,[1,2] rapid-acting[3] drug that, combined with Britannia's extensive Package of Care, can maintain your PD patients' independence.[4]

Prescribing information can be found overleaf

Britannia Pharmaceuticals

Britannia Pharmaceuticals is a trading name of Genus Pharmaceuticals Ltd

Confidence in consistent control

APO-go®

Version Number: APG.API.V7

ABBREVIATED PRESCRIBING INFORMATION

Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylaze 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 bases; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Caution should be exercised if prescribing apomorphine to pregnant women and women of childbearing age. Breast-feeding should be avoided during apomorphine HCl therapy. **Interactions:** Patients should be monitored for potential interactions during initial stages of apomorphine therapy. Particular caution should be given when apomorphine is used with other medications that have a narrow therapeutic window. It should be noted that there is potential for interaction with neuroleptic and antihypertensive agents. **Precautions:** Use with caution in patients with renal, pulmonary or cardiovascular disease, or who are prone to nausea or vomiting. Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients. Since apomorphine may produce hypotension, care should be exercised in patients with cardiac disease or who are taking vasoactive drugs, particularly when pre-existing postural hypotension is present. Neuropsychiatric disturbances are common in Parkinsonian patients. APO-go should be used with special caution in these patients. Apomorphine has been associated with somnolence and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with Parkinson's disease. Patients must be informed of this and advised to exercise caution whilst driving or operating machines during treatment with apomorphine. Haematology tests should be undertaken at regular intervals as with levodopa with given concomitantly with apomorphine. Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists, including apomorphine. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop at subcutaneous site of injection leading to areas of erythema, tenderness, induration and (rarely) ulceration. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "on" periods can be severe, and in a few patients may result in cessation of therapy. Postural hypotension is seen infrequently and is usually intransient. Transient sedation following each dose of apomorphine may occur at the start of therapy, but this usually resolves after a few weeks of treatment. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropyschiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia have been reported in patients receiving apomorphine and levodopa. Local and generalised rashes have been reported. Eosinophilia has occurred in only a few patients during treatment with apomorphine HCl. Patients treated with dopamine agonists, including apomorphine, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality (especially at high doses). Apomorphine is associated with somnolence. Breathing difficulties have been reported. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go opens (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.

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

Marketing Authorisation Numbers:
APO-go Ampoules: PL04483/0064
APO-go Pens: PL04483/0065
APO-go Pre filled syringes: PL05928/0025
Legal Category: POM
Date of last revision: July 2008

For further information please contact: Britannia Pharmaceuticals Limited, 41-51 Brighton Road, Redhill, Surrey RH1 6YS.

Adverse events should be reported.
Reporting forms and information can be found at www.yellowcard.gov.uk.
Adverse events should also be reported to Medical Information at Britannia at the above address or telephone 01737 773741 or e-mail: drugsafety@britannia-pharm.com

Version Number: APG.API.V7

Editorial board and contributors

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

Alasdair Coles is co-editor of ACNR. He is a University Lecturer in Neuroimmuniology at Cambridge University. He works on experimental immunological therapies in multiple sclerosis.

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

David J Burn is the editor of our Conference News Section and is Professor in Movement Disorder Neurology & Honorary Consultant, Newcastle General Hospital. He runs Movement Disorders clinics in Newcastle-upon-Tyne. Research interests include progressive supranuclear palsy and dementia with Lewy bodies. He is also involved in several drugs studies for Parkinson's Disease.

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

Alastair Wilkins is our Case Report Co-ordinator. He is Senior Lecturer in Neurology and Consultant Neurologist, University of Bristol. He trained in Neurology in Cambridge, Norwich and London. His research interests are the basic science of axon degeneration and developing treatments for progressive multiple sclerosis.

Nicki Cohen is ACNR's Neuropathology Editor. She is a Specialist Registrar in Neuropathology at Southampton and has a DPhil in Neuroscience. Her research interests lie in CNS stem cell biology, and the brain's response to injury.

Peter Whitfield is ACNR's Neurosurgery Editor. He is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Heather Angus-Leppan is ACNR's ABN representative on the Editorial Board. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

International editorial liaison committee

Professor Riccardo Soffietti, Italy: Chairman of the Neuro-Oncology Service, Dept of Neuroscience and Oncology, University and S. Giovanni Battista Hospital.

Professor Klaus Berek, Austria: Head of the Neurological Department of the KH Kufstein.

Professor Hermann Stefan, Germany: Professor of Neurology /Epileptology in the Department of Neurology, University Erlangen-Nürnberg.

Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Lyme Neuroborreliosis in Adults: Clinical Aspects

Lyme neuroborreliosis is caused by the tick-borne spirochete Borrelia burgdorferi (Bb) sensu lato. The Bb sensu lato complex consists of at least three human pathogenic species; Bb sensu stricto, B. garinii and B. afzelii. All are endemic in Europe, whereas Bb sensu stricto is the only species detected in North America. This may account for clinical differences in American and European neuroborreliosis. In this short review we convey basic facts, our own experience and some new knowledge of clinical manifestations, diagnostics, treatment and prognosis of Lyme neuroborreliosis in European adult patients.

Clinical manifestations

At least 80% of European patients with neuroborreliosis present with facial weakness due to facial neuritis, or lancinating pain, numbness and sometimes weakness in an extremity, the chest or abdomen due to spinal radiculitis, or a combination of these (Bannwarths syndrome).[1,2] More unusual symptoms are diplopia due to oculomotor, trochlear- or abducens neuritis,[3] visual loss due to retrobulbar optic neuritis,[4] hearing loss due to acoustic neuritis,[5] dizziness due to vestibular neuritis,[6] shortness of breath due to diaphragmatic paralysis,[7] and isolated muscle weakness and fasciculations due to selective involvement of motor neurons and motor roots.[8] A recent report describes a patient with an autoimmune-mediated motor neuropathy with conduction blocks and GM1 antibodies concomitant to, and probably triggered by infection with Bb.[9] Symptoms from the central nervous system are rare, but some patients may present with weakness and clumsiness of both legs due to myelitis,[10] or memory loss, confusion, unsteadiness, parkinsonism,[11] or opsoclonus myoclonus due to focal encephalitis.[12] Vasculitis may account for acute stroke like or relapsing symptoms with hemiparesis and aphasia.[13,14] Most patients with Lyme neuroborreliosis suffer from constitutional symptoms in addition to their neurological complaints, but it should be emphasized that headache, fatigue, paresthesias or malaise alone are not typical symptoms of Lyme neuroborrelisis.

The onset of Lyme neuroborreliosis is usually subacute with progression over weeks, so-called early or stage II Lyme neuroborreliosis. Some cases are self-limiting, even without treatment. Less than 10% of untreated cases progress slowly over months and years, so-called late, or stage III, Lyme neuroborreliosis.[1]

Laboratory confirmation

Due to the low yield from culture and polymerase chain reaction (PCR) in Lyme neuroborreliosis, we are left with indirect laboratory diagnostic methods. Both an elevated cell count in the cerebrospinal fluid (CSF) and elevated CSF-to-serum Bb antibody index, indicating intrathecal Bb antibody production, have to be present to confirm definite Lyme neuroborreliosis.

In day to day practice, however, diagnostics may be a challenge because the CSF Bb antibody index has a low sensitivity (about 75%) in patients with a symptom duration of less than six weeks,[15] and the CSF cell count may be normal in rare patients infected with certain genotypes of Bb.[16] It therefore seems reasonable to introduce the term possible Lyme neuroborreliosis. Suggested case definitions with two levels of diagnostic accuracy are presented in Table 1.

Different other laboratory tests such as CSF CXCL[13,17,18] LTT MELISA,[19] and Bb specific immune complexes,[20] may in the future be helpful diagnostic markers, but they need further validation.

Antibiotic treatment

All patients with Lyme neuroborreliosis should be treated with antibiotics to achieve rapid resolution of symptoms, and, theoretically, to prevent further dissemination

Dr Unn Ljøstad is a consultant clinical neurologist based at Sørlandet Hospital, Kristiansand, Norway. She will present her doctoral thesis on 'Lyme neuroborreliosis, diagnostics and treatment in European adult patients' later this year.

Dr Åse Mygland is Consultant Neurologist at Sørlandet Hospital Kristiansand and Assistant Professor at the Institute of Clinical Medicin, University of Bergen, Norway. She has a special interest in managing patients with neuromuscular and inflammatory neurological disorders.

Correspondence to:
Unn Ljøstad,
Department of Neurology,
Sørlandet Hospital,
Servicebox 416,
4604 Kristiansand, Norway.
Email. unn.ljostad@sshf.no

Table 1: Suggested case definitions

Definite neuroborreliosis All three criteria fulfilled	Possible neuroborreliosis Criterion 1 and one of a-d
1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons 2. CSF pleocytosis (>5 leucocytes/mm^3) 3. Intrathecal *Bb* antibody production	1. Neurological symptoms suggestive of Lyme neuroborreliosis without other obvious reasons a. CSF pleocytosis (> 5 leucocytes/mm^3) b. Intrathecal *Bb* antibody production c. *Bb* antibodies in serum d. Erythema migrans during the last four months

Table 2: Suggested treatment guidelines for European adult patients with Lyme neuroborreliosis

Drug	• First choice: o Oral doxycycline 200 mg daily • Alternative choices: o IV ceftriaxone 2 g daily o IV penicillin G 3 g X 3-4 o IV cefotaxime 2 g X 3
Treatment duration	2-4 weeks
Repeated course with a different drug	Should be restricted to patients with definite Lyme neuroborreliosis who do not improve after first course (exceptionally rare)
Post Lyme disease syndrome	Symptomatic treatment

and persistence of the infection. European Concerted Action on Lyme Borreliosis (EUCALB) suggests 14-30 days courses of IV ceftriaxone, IV penicillin, oral amoxicillin or oral doxycyline for early subacute Lyme neuroborreliosis, and 30 days courses of IV ceftriaxone or IV penicillin for late Lyme neuroborreliosis.[21] IV regimens with penicillin and ceftriaxone have similar efficacy, and it has recently been shown that oral doxycycline for 14 days is as efficient as IV ceftriaxone for 14 days in adult European patients.[2] We therefore suggest oral doxycyline as a first treatment choice for Lyme neuroborreliosis in adults, due to lower cost and easier administration. Suggested treatment guidelines are presented in Table 2. Enhanced therapeutic efficacy of extended treatment beyond two to three weeks is not well documented. The issue of longer treatment duration in all, or subgroups of, patients with Lyme neuroborreliosis, thus remains to be answered.

How to handle 'possible' Lyme neuroborreliosis

In our opinion patients who fulfill the criteria for possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. If one course does not lead to lasting improvement, a search for other causes of the symptoms should be sought.

Outcome after treatment

Outcome after treatment for Lyme neuroborreliosis is debated. A Swedish questionnaire follow-up study found persistent complaints 2.5 years post-treatment in 50% of patients who had experienced neuroborreliosis, as compared to 16% in control patients who had experienced erythema migrans.[22] Most of the complaints were subjective such as headache, attention problems, memory difficulties, depression and paresthesia. The real burden of remaining symptoms and neurological abnormalities after treatment for Lyme neuroborreliosis, as well as the pathophysiological mechanisms of post-Lyme disease syndrome, should be better charted in well designed studies. It seems clear that additional prolonged antibiotic treatment does not give any benefit in post-Lyme disease syndrome, and it should be remembered that treatments continued for months carry substantial risk for the patients.[23] Anecdotal reports of better response to long-term or repeated antibiotic treatment exist, but this could be due to placebo effect, which is known to occur in at least 30% of cases. A positive Bb antibody index may last for years and is not a suitable marker for treatment response.

Conclusion

We suggest two levels of diagnostic accuracy for clinical practice; definite and possible Lyme neuroborreliosis. Treatment with 2-4 weeks courses of IV ceftriaxone, penicilline or oral doxycycline are effective. We recommend oral doxycycline for two weeks as the first treatment choice. Patients with possible Lyme neuroborreliosis should be offered one, but not repeated courses of antibiotic treatment. Extensive antibiotic treatment is not recommended under any circumstances. The prognosis of neuroborreliosis and pathophysiology of post-treatment conditions need further studies.

We recommend oral doxycycline for two weeks as the first treatment choice. Enhanced therapeutic efficacy of extended treatment beyond two to three weeks is not well documented

References

1. Oschmann P, Dorndorf W, Hornig C, Schafer C, Wellensiek HJ, Pflughaupt KW. *Stages and syndromes of neuroborreliosis.* J.Neurol. 1998;245:262-72.
2. Ljostad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, Mygland A. *Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial.* Lancet Neurol. 2008;7(8):690-5.
3. Lell M, Schmid A, Stemper B, Maihofner C, Heckmann JG, Tomandl BF. *Simultaneous involvement of third and sixth cranial nerve in a patient with Lyme disease.* Neuroradiology. 2003;45:85-7.
4. Krim E, Guehl D, Burbaud P, Lagueny A. *Retrobulbar optic neuritis: a complication of Lyme disease?* J.Neurol.Neurosurg.Psychiatry. 2007;78:1409-10.
5. Walther LE, Hentschel H, Oehme A, Gudziol H, Beleites E. *Lyme disease--a reason for sudden sensorineural hearing loss and vestibular neuronitis?.* Laryngorhinootologie. 2003;82:249-57.
6. Hyden D, Roberg M, Odkvist L. *Borreliosis as a cause of sudden deafness and vestibular neuritis in Sweden.* Acta Otolaryngol.Suppl. 1995;520 Pt 2:320-2.:320-2.
7. Winterholler M, Erbguth FJ. *Tick bite induced respiratory failure. Diaphragm palsy in Lyme disease.* Intensive Care Med. 2001;27:1095.
8. Charles V, Duprez TP, Kabamba B, Ivanoiu A, Sindic CJ. *Poliomyelitis-like syndrome with matching magnetic resonance features in a case of Lyme neuroborreliosis.* J.Neurol.Neurosurg.Psychiatry. 2007;78:1160-1.
9. Rupprecht TA, Elstner M, Weil S, Pfister HW. *Autoimmune-mediated polyneuropathy triggered by borrelial infection?* Muscle Nerve. 2008;37:781-5.
10. Blanc F, Froelich S, Vuillemet F, Carre S, Baldauf E, de MS, Jaulhac B, Maitrot D, Tranchant C, de SJ. *Acute myelitis and Lyme disease.* Rev.Neurol.(Paris). 2007;163:1039-47.
11. Kohlhepp W, Kuhn W, Kruger H. *Extrapyramidal features in central Lyme borreliosis.* Eur.Neurol. 1989;29:150-5.
12. Skeie GO, Eldoen G, Skeie BS, Midgard R, Kristoffersen EK, Bindoff LA. *Opsoclonus myoclonus syndrome in two cases with neuroborreliosis.* Eur.J.Neurol. 2007;14:e1-e2.
13. Romi F, Krakenes J, Aarli JA, Tysnes OB. *Neuroborreliosis with vasculitis causing stroke-like manifestations.* Eur.Neurol. 2004;51:49-50.
14. May EF, Jabbari B. *Stroke in neuroborreliosis.* Stroke. 1990;21:1232-5.
15. Ljostad U, Skarpaas T, Mygland A. *Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis.* Eur.J.Neurol. 2007;14:873-6.
16. Strle F, Ruzic-Sabljic E, Cimperman J, Lotric-Furlan S, Maraspin V. *Comparison of findings for patients with Borrelia garinii and Borrelia afzelii isolated from cerebrospinal fluid.* Clin.Infect.Dis. 2006;43:704-10.
17. Rupprecht TA, Pfister HW, Angele B, Kastenbauer S, Wilske B, Koedel U. *The chemokine CXCL13 (BLC): a putative diagnostic marker for neuroborreliosis.* Neurology 2005;65:448-50.
18. Ljostad U, Mygland A. *CSF B - Lymphocyte Chemoattractant (CXCL13) in the early diagnosis of acute Lyme Neuroborreliosis.* J.Neurol. 2007.
19. Valentine-Thon E, Ilsemann K, Sandkamp M. *A novel lymphocyte transformation test (LTT-MELISA) for Lyme borreliosis.* Diagn.Microbiol.Infect.Dis. 2007;57:27-34.
20. Brunner M, Sigal LH. *Use of serum immune complexes in a new test that accurately confirms early Lyme disease and active infection with Borrelia burgdorferi.* J.Clin.Microbiol. 2001;39:3213-21.
21. Smith M, Gray J, Granstrom, M., Crawford R, and Gettinby G. *European Concerted Action on Lyme Borreliosis (EUCALB).* Stanek, G. and Gray, J. © EUCALB 1997-2007. European Union Concerted Action on Lyme Borreliosis . 2008. Ref Type: Electronic Citation.
22. Vrethem M, Hellblom L, Widlund M, Ahl M, Danielsson O, Ernerudh J, Forsberg P. *Chronic symptoms are common in patients with neuroborreliosis -- a questionnaire follow-up study.* Acta Neurol.Scand. 2002;106:205-8.
23. Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, Dattwyler R, Chandler B. *Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial.* Neurology 2003;60:1923-30.

Myasthenia Gravis and the Heart

Myasthenia gravis (MG) is well established as an autoimmune disorder with specific autoantibodies directed against the nicotinic acetylcholine receptor (AChR) in the neuromuscular junction. Involvement of the heart has been claimed and reported, but a causal connection between MG and altered cardiac function has not been found. This review summarises what is known about the possibility of heart involvement in MG.

Immunology

Whereas the AChR-antibody is the mainstay of MG, several other antibodies can be found. Some of these antibodies have been shown to react with cardiac muscle, thus being termed skeletal and heart reactive autoantibodies,[1] or striational antibodies. A proportion of this striational reactivity is due to antibodies against titin and the ryanodine receptor (RyR) found in the sarcoplasmic reticulum,[2] whereas other antibodies are claimed to react with myosin,[3] α-actin and actinin.[4] Non-striational antibodies have also been demonstrated in MG, directed against beta-adrenergic receptors[5] and against AChR of the muscarinic type.[6] Mygland demonstrated that the existence of heart muscle antibodies was related to type of MG, in finding such antibodies in MG-patients with thymoma and late-onset MG, but not in early onset MG. These heart muscle antibodies were shown to be specific for MG.[7] Lately, the discovery of antibodies to the muscle specific tyrosine kinase (MuSK)[8] has identified a subgroup of MG patients with rather distinct clinical characteristics. Antibodies to MuSK inhibit agrin-induced AChR-clustering, indicating a potential effect on agrin-dependent maintenance of AChRs at the neuromuscular junction. Cardiac function has not been examined specifically in MuSK-positive MG-patients.

The existence of all these antibodies – and antibodies not yet characterised – offers theoretical mechanisms for cardiac involvement in MG, by interfering with contractility, cardiac conduction, autonomous regulation or by an immunological attack on the myocardium, involving complement activation, infiltrates of inflammatory cells and with consequent necrosis.

Giant-cell myocarditis (GCM) is a condition showing a clear association to thymoma and in some cases to MG. GCM is characterised by degeneration and necrosis of heart muscle, and has been linked to IgG anti-cardiomyocyte antibodies.[9] GCM is however extremely rare, with only a few reported cases.

However, looking beyond the rare giant-cell myocarditis, the potential immunlogical mechanisms are at the present insufficiently correlated to clinical cardiological findings in MG patients.

Clinical findings

ECG

Changes in cardiac function as registered by changes in the ECG have been taken as a marker for MG-related cardiac disease. Hofstad found ECG abnormalities in 14 of 87 patients (16%), regarding the findings in twelve of these patients to be directly MG-related.[10] A larger study by Luomanmäki reported 97 MG-patients where 11% had abnormalities from concomitant heart disease, 9% had minor alterations (same rate as normal population) and 15% showed terminal notching of the QRS complex.[11] Later, Büyükötürk reported a higher frequency of QT-prolongation, right bundle branch block, sinus tachycardia and arrythmias than found in the normal population. Ashok found in 4 of 10 MG-patients flat to inverted T-waves, ST-depression and poor progression of R-waves in three precordial leads, all abnormalities reverting to normal following oral neostigmine.[12] On the other hand, a clinical study by Kornfeld[13] could not demonstrate any convincing ECG–changes in MG-patients. In conclusion, no distinct features of the ECG can be assigned to MG alone, and the significance of ECG in evaluation of MG-related cardiac disease is uncertain.

Clinical cardiac function

Few studies have clinically investigated cardiac function other than ECG in MG-patients. Johannessen found a reduced peak diastolic filling rate in 25 MG-patients without any known cardiovascular disease, hypertension, diabetes mellitus or pulmonary disease.[14] Ejection fraction was similar in patients and controls. Another study demonstrated a reduced global heart ejection fraction in 40% of MG patients without known cardiac disease after exercise, interpreted as a true association between MG and heart disease.[15] We have recently studied cardiac function in MG-patients without known cardiovascular disease, and found a reduced cardiac tissue velocity and strain (Owe et al, in press). These findings indicate subclinical alterations in cardiac function of some MG-patients. No modality of examination has been proven to be of value in routine examination of MG patients without symptoms of heart disease, and MG-patients do not have an increased risk of heart-related deaths.[16] There is a need for larger-scale clinical studies examining cardiac function in MG patients.

Post-mortem examinations and thymoma MG

The most convincing evidence for cardiac involvement in MG comes from autopsies. As early as 1901, Weigert demonstrated myocardial abnormalities in MG-patients. Later studies have confirmed the pathological findings in the hearts of MG-patients, focal inflammation and necrosis, and in the absence of atherosclerotic disease. The focal (spotty) appearance of the inflammation and necrosis bears resemblance to findings in skeletal muscles of MG-patients, and is believed to be due to lymphocytic infiltration of the myocardium. In a review from 1975, Gibson[17] found myocarditic changes in 28 of 75 patients with MG, the majority being associated with thymomas. Hofstad.[10] reported focal myocarditis in all three examined thymoma-MG patients. Among non-thymoma MG-patients, focal myocarditis or non-specific myocardial changes were found in three of five autopsies. Thus, thymomas are usually associated with myocardial involvement, but this can also occur in non-thymoma MG-patients.

Thymoma MG-patients are in addition prone to local thymoma- infiltration and invasion of the pericardium, myocardium, large vessels and other neighbouring structures, with the possible result of altered cardiac function. The observed high frequency of myocardial pathology in thymoma MG-patients could mean that an immunological attack with resulting inflammation and myocardial necrosis represents a paraneoplastic phenomenon related to the thymoma. Furthermore, thymoma patients have a broad range of autoantibodies, providing a theoretical mechanism for altered cardiac function, whether it is due to altered contractile force or altered conduction.

Effect of acetylcholine esterase inhibitors

The effect of acetylcholine esterase inhibitors (ACh-I) on cardiac function has been highlighted in several studies. Ashok found that non-specific ECG abnormalities in MG-patients reverted towards normal following neostigmine.[12] Johannesen found an increase in the peak diastolic filling rate in MG-patients following pyridostigmine.[14] We have demonstrated a normalizing of cardiac tissue velocity and

Jone Furlund Owe, MD, works in the Department of Clinical Medicine, Section for Neurology, University of Bergen, Norway.

Nils Erik Gilhus, MD, works in the Department of Neurology, Haukeland University Hospital, Bergen, Norway.

Correspondence to:
Department of Clinical Medicine, University of Bergen; and Department of Neurology, Haukeland University Hospital, Bergen, Norway.

strain following oral administration of pyridostigmine. It is unclear whether the effect of ACh-Is is a direct pharmacological effect on the myocardium, if it is an indirect effect altering the autonomous control of cardiac function or if it is due to down-modulation of receptors in MG-patients continuously treated with ACh-I, when the medication is withdrawn prior to the study. Anyhow, the effect of ACh-I on cardiac function in MG-patients, but not in controls, indicates that there is an ACh-I responsive alteration of cardiac function in some MG-patients.

Conclusions

When evaluating cardiac involvement in MG, a distinction has to be made between laboratory findings and clinical cardiac function. There is good evidence for myocardial pathology in MG patients, including a diversity of heart-reactive autoantibodies and focal inflammation with cellular infiltrates and myocardial necrosis. On the other hand, any firm clinical correlates to these findings have yet to be established. Clinical studies indicating a functional alteration in cardiac function are either too small, have conflicting results or cannot reliably distinguish any altered cardiac function caused by MG from altered function of other causes such as atherosclerotic disease. The indirect effect of MG, due to respiratory impairment and low muscle tone, can reduce venous return, altering cardiac haemodynamics. Hypoxia, hypercapnia, acidosis and associated respiratory infections in a myasthenic crisis could give rise to persisting myocardial changes. Suspected MG-related cardiac disease often occurs late in life, at a time when there is an increased risk of atherosclerotic disease. This creates a dilemma: excluding from the studies MG-patients with the slightest symptoms of cardiac disease may produce false negative findings, whereas inclusion of all MG-patients may obscure results due to presence of coexisting cardiovascular disease.

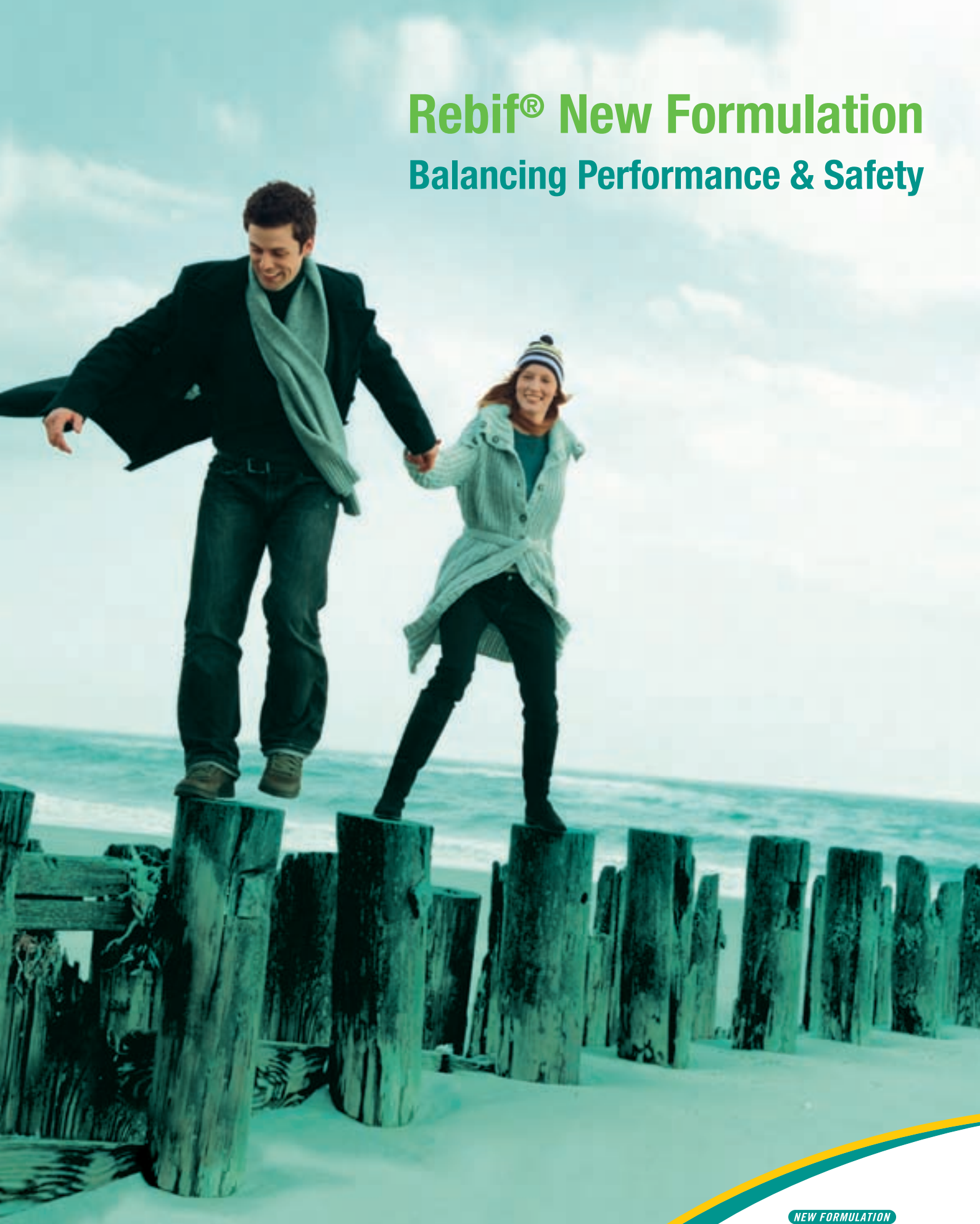
From the present evidence, one should regard thymoma MG-patients as a group at special risk for myocardial pathology. Heart symptoms in thymoma MG-patients should always be suspected as being caused by myocarditis (or pericarditis) and related to MG and autoimmunity. However, with available modalities of heart examination, there is, in our opinion, no need for MG-patients, regardless of any thymic pathology, to be examined routinely for heart disease unless cardiac symptoms arise.

References

1. Connor RI, Lefvert AK, Benes SC, Lang RW. *Incidence and reactivity patterns of skeletal and heart (SH) reactive autoantibodies in the sera of patients with myasthenia gravis.* J Neuroimmunol 1990;26(2):147-57.
2. Romi F, Skeie GO, Gilhus NE, Aarli JA. *Striational antibodies in myasthenia gravis: reactivity and possible clinical significance.* Arch Neurol 2005;62(3):442-6.
3. Penn AS, Schotland DL, Rowland LP. *Antibody to human myosin in man.* Trans Am Neurol Assoc 1969;94:48-53.
4. Ohta M, Ohta K, Itoh N, Kurobe M, Hayashi K, Nishitani H. *Anti-skeletal muscle antibodies in the sera from myasthenic patients with thymoma: identification of anti-myosin, actomyosin, actin, and alpha-actinin antibodies by a solid-phase radioimmunoassay and a western blotting analysis.* Clin Chim Acta 1990;187(3):255-64.
5. Xu BY, Pirskanen R, Lefvert AK. *Antibodies against beta1 and beta2 adrenergic receptors in myasthenia gravis.* J Neuroimmunol 1998;91(1-2):82-8.
6. Murie-Fernandez M, Gurpide A, de la CS, de CP. *Total remission of thymus carcinoma after treatment with intravenous immunoglobulin.* Clin Transl Oncol 2006;8(9):697-9.
7. Mygland A, Aarli JA, Hofstad H, Gilhus NE. *Heart muscle antibodies in myasthenia gravis.* Autoimmunity 1991;10(4):263-7.
8. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. *Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies.* Nat Med 2001;7(3):365-8.
9. HooKim K, deRoux S, Igbokwe A, Stanek A, Koo J, Hsu J, et al. *IgG anti-cardiomyocyte antibodies in giant cell myocarditis.* Ann Clin Lab Sci 2008;38(1):83-7.
10. Hofstad H, Ohm OJ, Mork SJ, Aarli JA. *Heart disease in myasthenia gravis.* Acta Neurol Scand 1984;70(3):176-84.
11. Luomanmaki K, Hokkanen E, Heikkila J. *Electrocardiogram in myasthenia gravis. Analysis of a series of 97 patients.* Ann Clin Res 1969;1(4):236-45.
12. Ashok PP, Ahuja GK, Manchanda SC, Jalal S. *Cardiac involvement in myasthenia gravis.* Acta Neurol Scand 1983;68(2):113-20.
13. Kornfeld P, Osserman KE. *Studies in myasthenia gravis. Evaluation of cardiac conduction.* J Mt Sinai Hosp N Y 1962;29:330-3.
14. Johannessen KA, Mygland A, Gilhus NE, Aarli J, Vik-Mo H. *Left ventricular function in myasthenia gravis.* Am J Cardiol 1992;69(1):129-32.
15. Rakocevic-Stojanovic V, Pavlovic S, Apostolski S, Lavrnic D, Vidakovic A, Kozarevic N. *Importance of radionuclide exercise ventriculography in patients with myasthena gravis.* 1996. Medicinska Istrazivanja 1996;30:17-19.
16. Owe JF, Daltveit AK, Gilhus NE. *Causes of death among patients with myasthenia gravis in Norway between 1951 and 2001.* J Neurol Neurosurg Psychiatry 2006;77(2):203-7.
17. Gibson TC. *The heart in myasthenia gravis.* Am Heart J 1975;90(3):389-96.

Rebif® New Formulation

Balancing Performance & Safety



Prescribing information is available on the adjacent page
Date of preparation: October 2007
REB07-0146

NEW FORMULATION
Rebif®
(interferon beta-1a)
sc injection

A balanced choice in MS

Management of Chronic Subdural Haematoma

Chronic subdural haematoma (CSDH) is one of the most common clinical entities encountered in daily neurosurgical practice. It generally occurs in the elderly population in whom age related reductions in brain volume with a corresponding increase in the size of the subdural space increase the vulnerability to this disease. Cerebral atrophy is also important in increasing the risk of CSDH in patients with epilepsy, alcoholism, Huntington's disease and those with overdrainage from a ventriculo-peritoneal shunt. Patients with a coagulopathy, including antiplatelet and antithrombotic therapy (e.g. aspirin, dypyridamole, warfarin and heparin) are also at an increased risk of CSDH.

Pathogenesis (Figure 1)

Two mechanisms, either alone or in combination, appear to play an aetiological role in the development of a CSDH.

1. An acute subdural haematoma that has not been evacuated may evolve into a CSDH. As the acute haematoma matures an inflammatory membrane forms and envelopes the clot. Repeated minor haemorrhages from neovascular structures in the membrane may contribute to haematoma expansion.[1] In addition the acute haematoma liquefies within days of the initial bleed. Fluid ingress, driven by an osmotic gradient generated by fibrinolytic products within the haematoma has been postulated to cause expansion during the conversion of an acute to a chronic subdural haematoma.[2,3]
2. Subdural hygroma formation secondary to a traumatic tear of the cortical arachnoid membrane allowing egress of CSF into the subdural space. The further expansion of the hygroma with conversion to a CSDH is attributed to repeated minor haemorrhages into the subdural collection from the membrane that surrounds the collection.[4] The demonstration of Beta–trace protein, a highly specific CSF marker, in the subdural fluid of the vast majority of patients with CSDH and all of the patients with a subdural hygroma offers support for this hypothesis.[5]

Presentation

Patients can present with one or more of the following clinical scenarios:

1. Symptoms and signs of raised intracranial pressure: headache, nausea, vomiting, impaired level of consciousness, papilloedema.
2. Focal neurological deficit secondary to compression of neuronal pathways: This depends on the location of the subdural haematoma (e.g hemiplegia with a posterior frontal haematoma, dysphasia with a dominant temporal haematoma, and sensory inattention with a parietal haematoma). In clinical practice deficits, including altered level of consciousness can fluctuate in severity leading to a delay in diagnosis.
3. Seizures: Focal or generalised.

Investigations

Computed tomography remains the preferred imaging modality and CSDH is classically described as a hypodense sickle-shaped extra axial fluid collection with evidence of surrounding mass effect. Where the haematoma evolves as a result of an acute bleed its density and appearance change with time in relation to the surrounding cortical surface. Three phases are described:

1. Hyperdense (0-7 days)
2. Isodense (1-3 weeks)
3. Hypodense (>3 weeks)

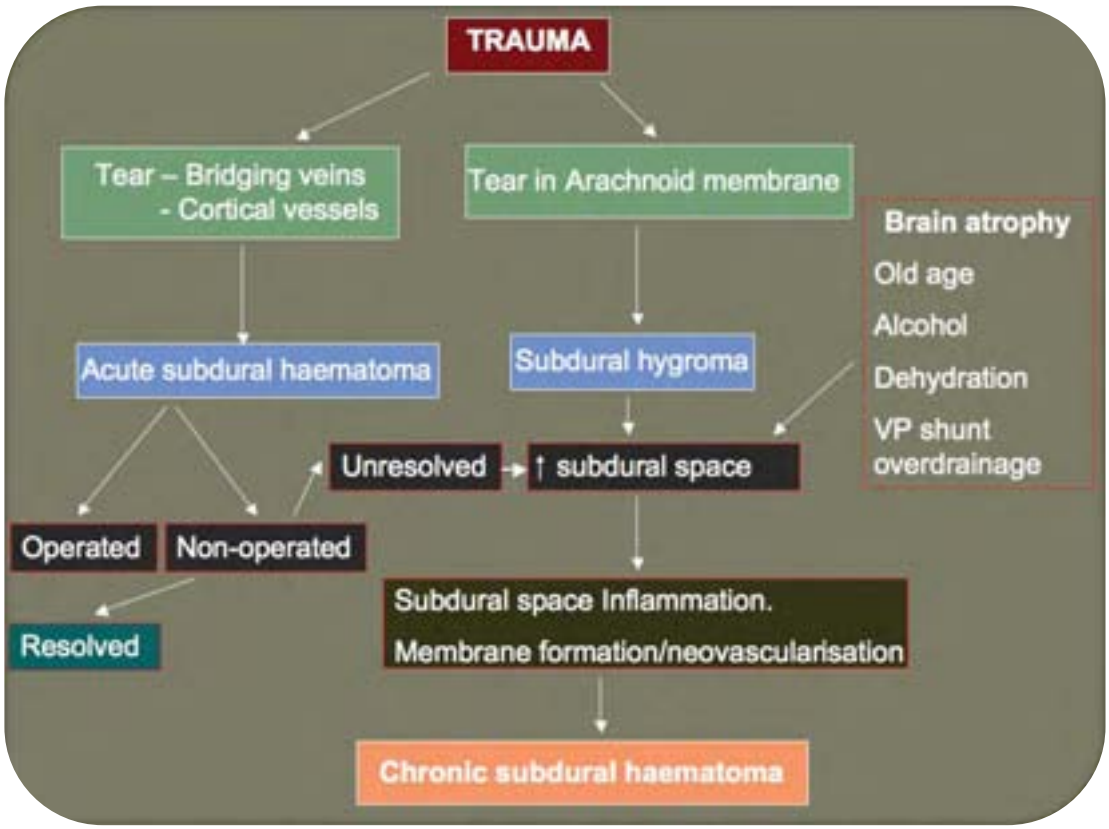


Figure 1: Diagram showing the pathogenesis of chronic subdural haematoma.

Puneet Plaha is a Specialist Registrar in Neurosurgery. He has completed three years of his South West Neurosurgical rotation at Derriford Hospital, Plymouth and is currently at Frenchay Hospital, Bristol. He graduated from JIPMER, University Hospital, Pondicherry in India. His main research interests are in surgery for movement disorders.

Dr Malhotra received his medical degree from the University of Virginia, where he was the J. Collins Scholar. He is currently serving as a resident in the Department of Neurosurgery at the Hospital of the University of Pennsylvania. Dr. Malhotra's primary research interests focus on restorative approaches to treat degenerative disc disease. More specifically, his interests focus on a tissue engineering approach to the development of treatments to restore native tissue mechanics of the spine while delivering therapeutic agents and supporting tissue regeneration.

Dr Heuer received his medical degree from the University of Pennsylvania in 2003. He has a Ph.D. in Cell and Molecular Biology. He is currently serving as a senior trainee in the Department of Neurosurgery at the Hospital of the University of Pennsylvania. Dr Heuer's research interests include the molecular mechanisms underlying genetic forms of epilepsy, surgery for movement disorders and epilepsy, foetal neurosurgery, and paediatric neuro-oncology.

Peter Whitfield is a Consultant Neurosurgeon at the South West Neurosurgery Centre, Plymouth. His clinical interests are wide including neurovascular conditions, head injury, stereotactic radiosurgery, image guided tumour surgery and lumbar microdiscectomy. He is an examiner for the MRCS and is a member of the SAC in neurosurgery.

Correspondence to:
Peter Whitfield,
South West Neurosurgery Centre,
Derriford Hospital,
Plymouth PL6 8DH.
Email. Peter.whitfield@
phnt.swest.nhs.uk

Once-Daily
AZILECT®
rasagiline

Simplicity

Azilect® 1mg tablets Prescribing information (Please refer to the Summary of Product Characteristics (SmPC) before prescribing) **Presentation:** Tablets containing 1mg rasagiline (as the mesilate). **Indication:** Treatment of idiopathic Parkinson's disease as monotherapy or as adjunct to levodopa in patients with end of dose fluctuations. **Dosage and administration:** Oral, 1mg once daily taken with or without food. Elderly: No change in dosage required. Children and adolescents (<18 years): Not recommended. Patients with renal impairment: No change in dosage required. Patients with hepatic impairment: Predominant hepatic metabolism. Do not use in patients with severe impairment. Avoid use in patients with moderate impairment. Use with caution in patients with mild impairment and stop if progresses to moderate. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic insufficiency. Co-administration of other monoamine oxidase (MAO) inhibitors is contraindicated due to risk of hypertensive crises. Concomitant pethidine treatment is contraindicated. Allow at least 14 days off rasagiline before using other MAO inhibitors or pethidine. **Special warnings and precautions:** Administer antidepressants with caution as serious adverse reactions have been reported with concomitant use of selective serotonin reuptake inhibitors, tricyclic and tetracyclic antidepressants, MAO inhibitors and a selective MAO-B inhibitor. Avoid concomitant use with fluoxetine or fluvoxamine. Leave at least five weeks between discontinuation of fluoxetine and initiation of treatment with rasagiline. Leave at least 14 days between discontinuation of rasagiline and initiation of treatment with fluoxetine or fluvoxamine. Administer potent CYP1A2 inhibitors with caution. Co-administration with dextromethorphan or sympathomimetics not recommended. Avoid use in patients with moderate hepatic impairment. Use caution in patients with mild hepatic impairment. Use with caution in pregnancy or lactation. There is an increased risk of skin cancer in Parkinson's disease, not associated with any particular drug. Suspicious skin lesions require specialist evaluation. **Undesirable effects in clinical trials**: Monotherapy: >1%: headache, flu syndrome, malaise, neck pain, dyspepsia, arthralgia, depression, conjunctivitis, allergic reaction, fever, angina pectoris, anorexia, leucopenia, arthritis, vertigo, rhinitis, contact dermatitis, vesiculobullous rash, skin carcinoma, hallucinations, urinary urgency. <1%: cerebrovascular accident, myocardial infarct. Adjunct therapy: >1%: abdominal pain, accidental injury, postural hypotension, constipation, vomiting, weight loss, dyskinesia, neck pain, anorexia, dry mouth, arthralgia, tenosynovitis, dystonia, abnormal dreams, ataxia, rash, hallucinations. <1%: angina pectoris, cerebrovascular accident, skin melanoma, confusion. Please refer to the SmPC for a full list of adverse events. **Basic NHS Price**: Azilect® (tablets) 1mg x 28 £70.72 **Legal category**: POM **Marketing Authorisation Number**: 1mg tablets (28 pack size) EU/1/04/304/003 **Marketing Authorisation Holder**: Teva Pharma GmbH, Kandelstr 10, D-79199 Kirchzarten Germany **Date last revised**: May 2008 **Further information available from**: Lundbeck Limited, Lundbeck House, Caldecotte Lake Business Park, Caldecotte, Milton Keynes, MK7 8LG

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

TEVA

Lundbeck

Job No. 1008/AZT/501/047

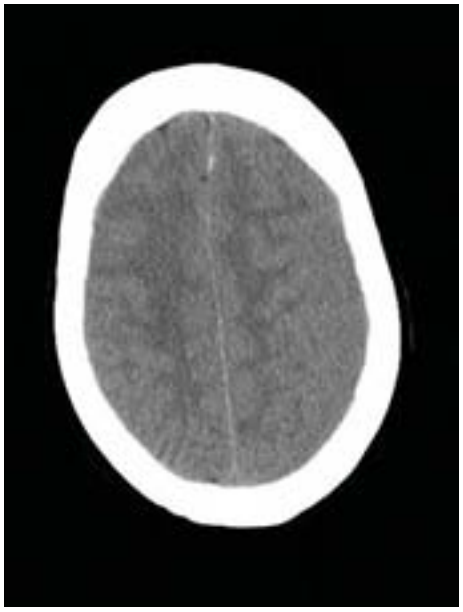


Figure 2: CT scan of a 62-year-old lady with leukemia and low platelets showing an isodense left sided chronic subdural haematoma. She presented with a history of headache. The density of the haematoma is the same as the adjacent cortical surface and can be easily missed.

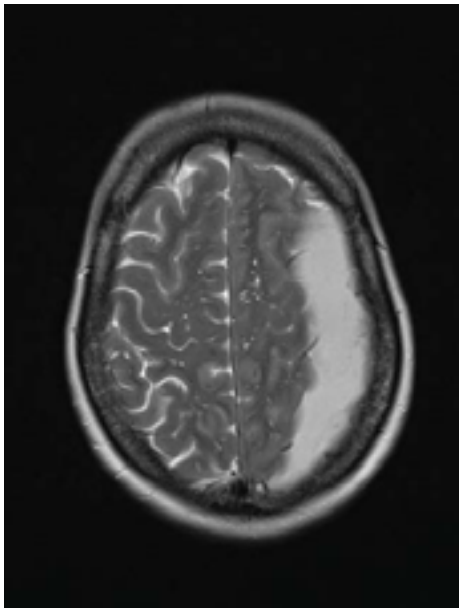


Figure 3: The same patient underwent an MRI scan which as shown on the T2 weighted sequence confirms a left sided chronic subdural haematoma.

In the majority of cases a CSDH is visualised as a mass comprising hypo and hyperdense signal characteristics. Bilateral isodense SDH's may result in a misdiagnosis due to difficulties in identifying cerebral cortex and the absence of midline shift (Figure 2). A contrast CT scan will show any enhancing membranes and can delineate the haematoma more precisely. MRI is also a useful adjunct in some cases. For the most part, T1 and T2 images both show the haematoma to be hyperintense relative to brain and CSF.[6] The change of signal intensity correlates with the length of time the haematoma has been present and the breakdown of blood in the haematoma capsule (Figure 3).

Treatment

Conservative and surgical approaches can be adopted when managing patients with a CSDH. A watch, wait and re-scan policy is usually recommended in asymptomatic or minimally symptomatic patients with a thin CSDH. Bed rest, osmotic diuretics and corticosteroids have been used although the evidence to support these measures is sparse.[7] For a patient with a symptomatic CSDH, surgery is the treatment of choice.

Preoperative workup

When undertaking surgery for a CSDH the coagulation status of the patient is of paramount importance. Aspirin should be stopped. In some cases the clinical status of the patient will necessitate urgent surgery despite aspirin treatment. If the patient's condition is stable, neurological deficits minor and the haematoma relatively small, surgery can be delayed for a few days to permit recovery of platelet function after cessation of antiplatelet therapy.

Another important factor in the treatment decision making process is the patient's coagulation status especially with the widespread use of therapeutic blood thinning agents. Warfarin therapy poses specific problems. Historically, warfarin reversal comprised oral or i.v. Vitamin K administration supplemented with fresh frozen plasma. Such a process can lead to unacceptable delays in performing emergency surgery while FFP is obtained, thawed, administered and haematological parameters rechecked. Complete and rapid reversal of warfarin over- anticoagulation is better achieved with 5 or 10mg of intravenous vitamin K and II, VII, IX and X factor concentrate (Beriplex™).[8,9]

Surgical options

The surgical approaches to the management of patients with CSDH are mainly limited to burrhole drainage, twist drill drainage and craniotomy. A small craniectomy has also been advocated as an alternative approach. Combining each technique with the use of intraoperative irrigation and/or post-operative drainage provides a variety of treatment options.

Surgical Techniques

Chronic SDHs are most commonly treated by burr hole evacuation. The number and location of the burr holes depends upon the size and location of the haematoma as determined by CT scan. Two burr holes located along the same line as the incision of a trauma flap are commonly employed. Care must be taken to secure any dural bleeding. The distinctive grey encapsulating membrane is opened to permit drainage of the liquefied haematoma. This is often under considerable initial pressure. Occasional conversion to a craniotomy is required if a substantial solid component persists. Irrigation of the subdural space, facilitated by the use of a soft Jacques catheter, is commonly performed to facilitate evacuation.

Twist drill craniostomy has been advocated in search of a less invasive treatment option with a skull opening usually less than 5mm. However, irrigation through such a small aperture is difficult. A craniotomy permits fluid evacuation and partial removal of the haematoma membrane in patients with recurrent, persistent chronic subdural haematomas.[10] A small craniectomy is an alternative that enables the significance of post-operative collections to be assessed by palpation and treated by percutaneous aspiration. A valveless subdural-peritoneal conduit fashioned from a peritoneal catheter with side holes cut for the subdural space and securely anchored to the galea can be useful in the treatment of patients with an atrophic brain where persistence of the subdural collection occurs despite recent drainage.

Weigel et al. analysed 48 publications (1981-2001) in a comprehensive meta-analysis comparing the outcome of various surgical techniques.[11] A wide range of cure, recurrence and mortality rates were found with each procedure. Overall, there was no significant difference in mortality between the three techniques. Mortality of up to 11% was noted. The morbidity from a craniotomy was reported to be higher than drainage procedures. Comparison between burrhole drainage and twist drill craniostomy revealed a higher recurrence rate with a twist drill approach.

Irrigation and drainage

The use of intraoperative irrigation with warm isotonic saline or artificial CSF until the effluents are clear is widespread. No significant differences were reported in the patients who received irrigation compared with those who did not in several series.[12-15] In a twist drill series, irrigation was found to improve the recurrence rate from 29.2% to 6.7%.[16] In contrast a lower recurrence rate has been reported in a more recent series in patients in whom intra-operative irrigation was not used.[17]

The use of closed post-operative subdural space drainage has long been considered. Some prospective studies showed no beneficial effect,[10,18,19] whereas other authors report lower recurrence rates with the use of post-operative drains.[20] In patients undergoing twist drill craniostomy, post-operative drainage did appear to reduce the recurrence rate from 68% to 9% in a meta-analysis.[11] The use of a closed subgaleal drainage system has also been reported.[21] Whilst there are no reports of a proven increased risk of infection with drains, this concern must exist.

Peri-operative continuous inflow and outflow irrigation with Ringer's lactate solution after evacuation of the haematoma has been reported to reduce the recurrence risk in a small prospective randomised study.[22] However the differences did not reach statistical significance (1/19 vs 4/18). A retrospective comparison of post operative inflow and outflow drainage with burr hole evacuation +/- closed drainage and craniotomy showed significantly lower recurrence rate in patients with continuous inflow-outflow drainage.[23] Despite these small studies such techniques have not been widely adopted.

Complications

Postoperative CT scans to follow the progress of patients have shown that residual haematoma is

quite common regardless of the operative procedure used. However, in the majority of cases, removal of most of the haematoma will result in alleviation of symptoms and any residual haematoma will gradually reabsorb over a period of weeks.

The incidence of true reaccumulation or recurrence of the haematoma varies with the chosen surgical intervention as discussed above. Many risk factors for recurrence of CSDH have been reported previously, including advanced age, bleeding tendency, brain atrophy, haematoma density, alcohol abuse, postoperative subdural air accumulation, bilateral CSDH and arachnoid cyst. More recently the presence of high concentrations of beta trace protein in the subdural fluid at the time of initial surgery signifying CSF leakage into the subdural space, and high levels of interleukin-6 signifying inflammation of membranes or enhanced expression of VEGF and bFGF in the outer membrane may result in a higher risk of a recurrence.[5,24]

Other complications include seizures, pneumocephalus, subdural empyaema and rarely intracranial haemorrhage. Extracranial complications such as post-operative pneumonia and pulmonary embolism may also occur in patients with a CSDH. Following surgery the risks and benefits of antiplatelet and anticoagulant therapy need careful consideration on a case by case basis before reintroduction.

Summary

The diagnosis of chronic subdural haematoma should be considered in any elderly patient presenting with focal neurological signs or with any suggestion of raised intracranial pressure. For the majority of patients surgical drainage of a symptomatic chronic subdural haematoma is readily performed with a relatively low risk of operative morbidity and mortality. Most patients make a satisfactory recovery. Reaccumulation is the most common sequelae and can be troublesome in a small minority of patients. A number of operative variations have been reported to try and minimise this risk, however the evidence to support any specific operative technique is not persuasive. The use of post-operative anticoagulants and antiplatelet agents needs careful consideration particularly in patients with a history of haematoma recurrence.

References

1. Stoodley M, Weir B. *Contents of chronic subdural hematoma.* Neurosurg Clin N Am 2000;11(3):425-34.
2. Drapkin AJ. *Chronic subdural hematoma: pathophysiological basis for treatment.* Br J Neurosurg 1991;5(5):467-73.
3. Weir B, Gordon P. *Factors affecting coagulation: fibrinolysis in chronic subdural fluid collections.* J Neurosurg 1983;58(2):242-5.
4. Lee KS. *Natural history of chronic subdural haematoma.* Brain Inj 2004;18(4):351-8.
5. Kristof R, Grimm J, Stoffel-Wagner B. *Cerebrospinal fluid leakage into the subdural space: possible influence on the pathogenesis and recurrence frequency of chronic subdural haematoma and subdural hygroma.* J Neurosurg 2008;108(2)(Feb):275-80.
6. Hosoda K, Tamaki N, Masumura M, Matsumoto S, *Maeda F. Magnetic resonance images of chronic subdural hematomas.* J Neurosurg 1987;67(5):677-83.
7. Sun TF, Boet R, Poon WS. *Non-surgical primary treatment of chronic subdural haematoma: Preliminary results of using dexamethasone.* Br J Neurosurg 2005;19(4):327-33.
8. Baglin TP, Keeling DM, Watson HG. *Guidelines on oral anticoagulation (warfarin): third edition--2005 update.* Br J Haematol 2006;132(3):277-85.
9. Evans G, Luddington R, Baglin T. *Beriplex P/N reverses severe warfarin-induced overanticoagulation immediately and completely in patients presenting with major bleeding.* Br J Haematol 2001;115(4):998-1001.
10. Markwalder TM. *Chronic subdural hematomas: a review.* J Neurosurg 1981;54(5):637-45.
11. Weigel R, Schmiedek P, Krauss JK. *Outcome of contemporary surgery for chronic subdural haematoma: evidence based review.* J Neurol Neurosurg Psychiatry 2003;74(7):937-43.
12. Iwadate Y, Ishige N, Hosoi Y. *Single burr hole irrigation without drainage in chronic subdural hematoma.* Neurol Med Chir (Tokyo) 1989;29(2):117-21.
13. Benzel EC, Bridges RM, Jr., Hadden TA, Orrison WW. *The single burr hole technique for the evacuation of non-acute subdural hematomas.* J Trauma 1994;36(2):190-4.
14. Matsumoto K, Akagi K, Abekura M, Ryujin H, Ohkawa M, Iwasa N, et al. *Recurrence factors for chronic subdural hematomas after burr-hole craniostomy and closed system drainage.* Neurol Res 1999;21(3):277-80.
15. Suzuki K, Sugita K, Akai T, Takahata T, Sonobe M, Takahashi S. *Treatment of chronic subdural hematoma by closed-system drainage without irrigation.* Surg Neurol 1998;50(3):231-4.
16. Aoki N. *Subdural tapping and irrigation for the treatment of chronic subdural hematoma in adults.* Neurosurgery 1984;14(5):545-8.
17. Kuroki T, Katsume M, Harada N, Yamazaki T, Aoki K, Takasu N. *Strict closed-system drainage for treating chronic subdural haematoma.* Acta Neurochir (Wien) 2001;143(10):1041-4.
18. Markwalder TM, Seiler RW. *Chronic subdural hematomas: to drain or not to drain?* Neurosurgery 1985;16(2):185-8.
19. Laumer R, Schramm J, Leykauf K. *Implantation of a reservoir for recurrent subdural hematoma drainage.* Neurosurgery 1989;25(6):991-6.
20. Wakai S, Hashimoto K, Watanabe N, Inoh S, Ochiai C, Nagai M. *Efficacy of closed-system drainage in treating chronic subdural hematoma: a prospective comparative study.* Neurosurgery 1990;26(5):771-3.
21. Gazzeri R, Galarza M, Neroni M, Canova A, Refice GM, Esposito S. *Continuous subgaleal suction drainage for the treatment of chronic subdural haematoma.* Acta Neurochir (Wien) 2007;149:973-4.
22. Ram Z, Hadani M, Sahar A, Spiegelmann R. *Continuous irrigation-drainage of the subdural space for the treatment of chronic subdural haematoma. A prospective clinical trial.* Acta Neurochir (Wien) 1993;120(1-2):40-3.
23. Hennig R, Kloster R. *Burr hole evacuation of chronic subdural haematomas followed by continuous inflow and outflow irrigation.* Acta Neurochir (Wien) 1999;141(2):171-6.
24. Hong H, KIM Y, Yi Y, Ko Y, Oh S, Kim J. *Role of angiogenic growth factors and inflammatory cytokine on recurrence of chronic subdural haematoma.* Surg Neurol 2008;17(Apr):(Epub ahead of print).

Epilepsy and Hippocampal Sclerosis: Cause or Effect?

Hippocampal sclerosis (HS) is the most common pathological finding in mesial temporal lobe epilepsy,[1] accounting for approximately 70% of cases in patients undergoing surgery for drug-resistant partial seizures.[2] Other focal lesions associated with partial epilepsy are listed in Table 1. The broader term mesial temporal sclerosis (MTS) acknowledges the frequent involvement of neighbouring limbic structures including the amygdala and parahippocampal gyrus.

Despite the strong association between hippocampal sclerosis and temporal lobe epilepsy, it remains unclear whether or not the relationship is causal – or if both conditions might reflect an underlying developmental abnormality of the hippocampus. In this article we will briefly review the pathological features of hippocampal sclerosis, before moving on to discuss some of the relevant experimental and clinical evidence.

Hippocampal sclerosis

The typical MRI features of hippocampal sclerosis, also known as Ammon's horn sclerosis (AHS), are unilateral volume loss and increased signal intensity on T2-weighted images. There is no sex or side preference and a proportion of cases are bilateral. Macroscopically the hippocampus is firm and shrunken, sometimes with visible collapse of the CA1 subfield (Sommer's sector). Microscopic findings include a characteristic pattern of neuronal loss and reactive gliosis (Figure 1) that varies in severity from case to case (Table 2).[3] The mechanism of neuronal loss and selective vulnerability in MTS is likely to be excessive release of the excitatory neurotransmitters glutamate and aspartate, acting at calcium-permeable NMDA and AMPA receptors ('excitotoxicity').[4] This leads to intense depolarisation and calcium overload which triggers multiple cell death pathways. In addition to neuronal loss and gliosis, two commonly associated findings are mossy fibre sprouting and granule cell dispersion (Table 3).

Aetiology and pathogenesis

Several animal models of limbic status epilepticus demonstrate that HS can be acquired – and the pathological features in many cases are similar to those seen in humans.[5] MRI and post-mortem studies also confirm that acute hippocampal damage may follow status epilepticus.[6,7] An influential hypothesis suggests that an initial precipitating insult (IPI) in childhood such as a febrile convulsion may injure the hippocampus and that this 'first hit' at a critical period of development may act as a template for progressive neuronal loss and gliosis.[8] It has been known for many years that more than half of patients with HS and temporal lobe epilepsy have a history of febrile convulsion or status epilepticus in infancy.[1,9] This is typically followed by a variable 'latent interval' of around 7-10 years before the onset of spontaneous seizures. MRI studies in children with prolonged febrile convulsions have demonstrated acute changes in the hippocampus consistent with neuronal injury and oedema. Some follow-up studies have shown subsequent hippocampal atrophy[7] or hippocampal sclerosis[6] although the presence of a pre-existing abnormality cannot be excluded. It is important to note that most of these children do not develop epilepsy[10] and that at least a third of patients with hippocampal sclerosis have no documented IPI.

Do seizures damage the brain?

It is often said that 'seizures beget seizures', but it has been difficult to demonstrate conclusively that patients with pharmacoresistant temporal lobe epilepsy suffer ongoing hippocampal damage. Some studies have shown a gradual deterioration in hippocampal volume, metabolism or memory performance over time[11] or evidence of progres-

Table 1: Common pathological findings in epilepsy surgical specimens

- Hippocampal sclerosis (HS)
- Malformations of cortical development (MCD)
  – focal cortical dysplasia (FCD)
  – mild malformations of cortical development (formerly 'microdysgenesis')
- Low grade glioneuronal tumours
  – ganglioglioma
  – dysembryoplastic neuroepithelial tumour (DNT)
- Vascular / traumatic lesions
- Dual pathology
  – usually mild HS in combination with a second pro-epileptogenic lesion

Table 2: Simple classification of hippocampal sclerosis

Subtype	Main pathological features
Classical	Neuronal loss and gliosis mainly in CA1, CA3 and end-folium
Total	Severe neuronal loss in all hippocampal subfields and the dentate gyrus
End-folium	Neuronal loss and gliosis restricted to the hilum of the dentate gyrus

Table 3: Features commonly associated with hippocampal sclerosis

Feature	Description	Possible significance
Mossy fibre sprouting (MFS)	New axons arising from granule cells extend upwards into the molecular layer of the dentate gyrus. This can be demonstrated by immunostaining for the neuropeptide dynorphin (see Figure 1F).	May contribute to epileptogenesis by forming potentially self-excitatory connections within the dentate gyrus. However, inhibition of MFS in experimental models does not prevent spontaneous seizures.
Granule cell dispersion (GCD)	Increased width of granule cell layer, which is normally 4-5 cells thick, but is more than 10 cells deep in at least 40% of HS cases. Cells often have a spindle-cell appearance, reminiscent of migrating neurons (see Figure 1G-I).	Also occurs in the opposite side, therefore may be a response to generalised seizure activity rather than signifying damage. Some animal models show increased neurogenesis in the subgranular layer, with upward migration of new neurons along radial glia.

Dr Paul Johns is a specialist registrar in neuropathology at the National Hospital for Neurology and Neurosurgery, Queen Square. His research interests have included neuroprotection in acute cerebral ischaemia and the pathology of focal epilepsy. In 2006 he won the Intercapital Prize in Epileptology.

Dr Maria Thom is a Senior Lecturer at the Institute of Neurology, Queen Square and an Honorary Consultant Neuropathologist at the National Hospital for Neurology and Neurosurgery. Her research has focused on the pathology of focal epilepsies.

Correspondence to:
Dr Paul Johns,
Specialist Registrar,
Division of Neuropathology,
National Hospital for Neurology and Neurosurgery,
Institute of Neurology,
Queen Square,
London WC1N 3BG, UK.
Email. paul.johns@uclh.org
Tel. 0207 829 8731
Fax. 0207 676 2157

ABBREVIATED PRESCRIBING INFORMATION
Zonegran® (zonisamide)
Please refer to the SmPC before prescribing.
Presentation: Hard capsules containing 25 mg, 50 mg or 100 mg zonisamide. ***Indication:*** Adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation. ***Dose and administration: Adult:*** Zonegran must be added to existing therapy. Initial daily dose is 50 mg in two divided doses. After one week, increase to 100 mg daily and then at one weekly intervals, in 100 mg increments. Consider two weekly intervals in renal or hepatic impairment and patients not receiving CYP3A4-inducing agents. Zonegran can be administered once or twice daily after the titration phase. Withdraw gradually. ***Elderly and patients with renal or hepatic impairment:*** Caution (see SmPC). Not recommended in severe hepatic impairment. ***Children and adolescents under 18 years:*** Not recommended. ***Contra-Indications:*** Hypersensitivity to zonisamide, sulphonamide or any excipient. ***Pregnancy:*** Zonegran must not be used during pregnancy unless clearly necessary in the opinion of the physician, and only if potential benefits justify risk to the foetus. Specialist advice should be given to women who are likely to become pregnant in order to consider the optimal treatment during pregnancy. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. ***Lactation:*** Zonisamide is excreted into breast milk. A decision must be made to either discontinue Zonegran or stop breast-feeding. Breast-feeding should not be resumed until one month after stopping Zonegran. ***Warnings and Precautions:*** Serious rashes occur in association with Zonegran therapy, including cases of Stevens-Johnson syndrome. Zonegran contains a sulphonamide group. Serious immune based adverse reactions are associated with the sulphonamide group, e.g. rash, allergic reaction, major haematological disturbances including aplastic anaemia, which very rarely can be fatal. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Kidney stones have occurred. Use with caution in patients with risk factors for nephrolithiasis, including prior stone formation, a family history of nephrolithiasis and hypercalcuria. Use with caution in patients treated with carbonic anhydrase inhibitors, e.g. topiramate. Decreased sweating, elevated body temperature and heat stroke have been reported. Patients should maintain hydration and avoid excessive temperatures. Monitor pancreatic lipase and amylase levels in patients taking Zonegran who develop clinical signs and symptoms of pancreatitis, and consider discontinuation in absence of another cause. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage, e.g. serum creatine phosphokinase and aldolase levels, and consider discontinuation. Zonegran 100 mg hard capsules contain E110, which may cause allergic reactions. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. ***Drug Interactions:*** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. ***Side effects:*** The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance: Very common effects (≥1/10): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence, diplopia, decreased bicarbonate. Common effects (≥1/100, <1/10): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon (≥1/1000, <1/100): pneumonia, urinary tract infection, hypokalemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. Very Rare (<1/10,000 including isolated reports): agranulocytosis, aplastic anemia, leucocytosis, leucopenia, lymphadenopathy, pancytopenia, thrombocytopenia, metabolic acidosis, hallucination, amnesia, coma, grand mal seizure, myasthenic syndrome, neuroleptic malignant syndrome, status epilepticus, dyspnoea, pneumonia aspiration, respiratory disorder, pancreatitis, hepatocellular damage, anhidrosis, erythema multiforme, pruritis, Stevens-Johnson syndrome, rhabdomyolysis, hydronephrosis, renal failure, urine abnormality, blood creatine phosphokinase increased, blood creatinine increased, blood urea increased, liver function tests abnormal, heat stroke. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged 65 years or older report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. ***Legal Category:*** POM. ***Presentation:*** PVC/PCTFE/aluminium blisters. ***Basic UK NHS cost:*** Zonegran 25 mg: packs of 14 £8.82, Zonegran 50 mg: packs of 56 £47.04, Zonegran 100 mg: packs of 56 £62.72. ***Irish price to wholesaler:*** Zonegran 25 mg: packs of 14 €10.95, Zonegran 50 mg: packs of 56 €58.07, Zonegran 100 mg: packs of 56 €77.59. ***Marketing authorisation numbers:*** Zonegran 25 mg 14 capsules: EU/1/04/307/001, Zonegran 50 mg 56 capsules: EU/1/04/307/003, Zonegran 100 mg 56 capsules: EU/1/04/307/004. ***Marketing authorisation holder:*** Eisai Ltd. ***Further Information from/Marketed by:*** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE. ***Date of preparation:*** June 2008.

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

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

Date of preparation: September 2008. Z2191 09/08

Advancing Epilepsy Management

Eisai

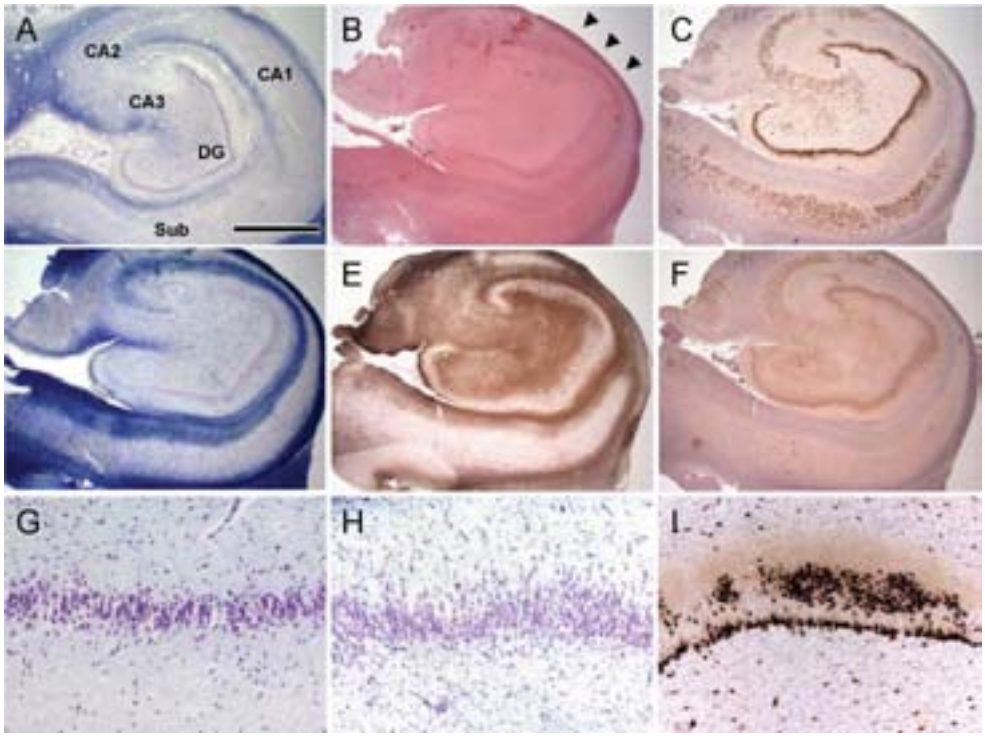


Figure 1: Microscopic appearances of (A) normal hippocampus and (B-I) hippocampal sclerosis.
(A) Normal hippocampal anatomy. CA1-CA3=Ammon's horn (Latin: cornu ammonis). DG=dentate gyrus. Sub=subiculum.
(B) In hippocampal sclerosis, collapse of CA1 (arrows) is evident even at low power.
(C) Selective neuronal drop-out is highlighted by immunohistochemical preparations for the neuronal marker NeuN.
(D) Reduced width of CA1 is more striking on a myelin preparation (Luxol fast blue/cresyl violet).
(E) Reactive gliosis/astrocytosis generally parallels the degree of neuronal loss, demonstrated here (dark brown staining) by immunohistochemistry for the astrocytic marker glial fibrillary acidic protein (GFAP).
(F) Mossy fibre sprouting is identified in diagnostic practice as a band of dynorphin-immunoreactivity (light brown) in the supragranular layer of the dentate gyrus.
(G) The normal dentate gyrus contains a compact and sharply-defined layer of granule cells.
(H) Granule cell dispersion is seen in at least 40% of HS cases.
(I) The granule cell layer is focally bilaminar in up to 10% of cases, illustrated here by immunostaining for the neuronal marker NeuN. [Scale bar: A-F=2mm; G-I=200μm].

sive atrophy in the contralateral hemisphere[12] but the confounding effects of long-term exposure to antiepileptic drugs and seizure-associated head injuries should be borne in mind. In general, prospective MRI studies have failed to show a consistent relationship between the degree of hippocampal sclerosis and the duration/severity of epilepsy or the total number of generalised seizures.[13] Furthermore, a quantitative post-mortem study has identified a subgroup of patients with a life-long history of frequent seizures (including status epilepticus) but no significant neuronal loss in the hippocampus.[14] Clearly, seizures do not inevitably damage the brain – and it is far from clear that hippocampal sclerosis worsens over time.

Developmental theories

An alternative possibility is that a pre-existing temporal lobe abnormality leads to hippocampal sclerosis in adulthood and also increases risk of febrile convulsions in the early years of life. Examination of resected material in HS patients shows evidence for the persistence of Cajal-Retzius cells in the superficial temporal cortex and alterations within the reelin signalling pathway, both of which may signify a disturbance of neuronal migration.[15] Further evidence to support this contention, derived from patients with pathologically-confirmed HS, includes: an increased incidence of subtle hippocampal malformations; excess ectopic white matter neurons in the mesial temporal lobe; and association with other lesions that may have a malformative origin (including low-grade glioneuronal tumours).[16] Furthermore, subtle hippocampal malformations have been found in relatives of patients with HS (compared to age-matched controls) most of whom did not have a history of febrile convulsions or HS themselves.[17] A maldevelopmental origin would perhaps also help to explain why hippocampal sclerosis is often unilateral.

Concluding remarks: chicken or egg?

The association between temporal lobe epilepsy and hippocampal sclerosis has been recognised for over a century, but despite many decades of basic and clinical research it is still not possible to assign an arrow of causality. One explanation is that hippocampal sclerosis may represent a phenotypically-similar manifestation of a heterogeneous group of pathologies with diverse pathogenesis, derived from a complex interplay of numerous factors (including genetic, developmental and environmental components). These same factors may also explain why some people are susceptible to seizure-associated hippocampal damage and others appear to be resistant. It is hoped that more light may be shed on this intriguing issue over the coming decades, perhaps facilitated by large-scale prospective neuroimaging studies which can be used to follow its evolution during the early years of life.

References

1. Margerison JH, Corsellis JAN. *Epilepsy and the temporal lobes: a clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes.* Brain 1966;89:499-530.
2. Zentner J, Hufnagel A, Wolf HK, et al. *Surgical treatment of temporal lobe epilepsy: clinical, radiological, and histopathological findings in 178 patients.* J Neurol, Neurosurg and Psych 1995;58:666-73.
3. Thom M. *Recent advances in the neuropathology of focal lesions in epilepsy.* Expert Rev Neurother 2004;4(6):973-84.
4. Meldrum BS. *Excitotoxicity and selective neuronal loss in epilepsy.* Brain Pathol 2008;3(4):405-12.
5. Coulter DA, McIntyre DC, Löscher W. *Animal models of limbic epilepsies: what can they tell us?* Brain Pathol 2002;12(2):240-56.
6. Provenzale JM, Barboriak DP, VanLandingham K, et al. *Hippocampal MRI signal hyperintensity after febrile status epilepticus is predictive of subsequent mesial temporal sclerosis.* AJR 2007;190:976-83.
7. Scott RC, King MD, Gadian DG, et. Al. *Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study.* Brain 2003;126:2551-7.
8. Mathern GW, Adelson PD, Cahcal LD, et al. *Hippocampal neuron damage in human epilepsy: Meyer's hypothesis revisited.* Prog Brain Res 2002;135:237-51.
9. ILAE Commission report. *Mesial temporal lobe epilepsy with hippocampal sclerosis.* Epilepsia 2004;45(6):695-714.
10. Lado FA, Dankar R, Lowenstein D, et al. *Age-dependent consequences of seizures: relationship to seizure frequency, brain damage, and circuitry reorganisation.* Mental retardation and developmental disabilities 2000;6:242-52.
11. Jokeit H, Ebner A, Arnold S, et al. *Bilateral reductions of hippocampal volume, glucose metabolism and Wada hemispheric memory performance are related to the duration of mesial temporal lobe epilepsy.* J Neurol 1999;246:926-33.
12. Araújo D, Santos AC, Velasco RT, et al. *Volumetric evidence of bilateral damage in unilateral mesial temporal lobe epilepsy.* Epilepsia 2006;47(8):1354-9.
13. Cendes F, Andermann F, Gloor P, et al. *Atrophy of mesial structures in patients with temporal lobe epilepsy: cause or consequence of repeated seizures.* Ann Neurol 1993;34:795-801.
14. Thom M, Zhou J, Martinian L, et al. *Quantitative post-mortem study of the hippocampus in chronic epilepsy: seizures do not inevitably cause neuronal loss.* Brain 2005;128:1344-57.
15. Blümcke I, Thom M, Wiestler OD. *Ammon's horn sclerosis: a maldevelopmental disorder associated with temporal lobe epilepsy.* Brain Pathol 2002;12(2):199-211.
16. Fisher PD, Sperber EF, Moshé SL. *Hippocampal sclerosis revisited.* Brain and development 1998;20(8):563-73.
17. Fernandez G, Effenberger O, Vinz B, et al. *Hippocampal malformation as a cause of familial febrile convulsions and subsequent hippocampal sclerosis.* Neurology 1998;50:909-17.

Charles Bonnet's Syndrome

Drs Kathryn Bundle, Mayur Bodani, and Lal Landham, in *ACNR*, June 2007 described Pregabalin in the treatment of visual hallucinations in Charles Bonnet Syndrome (CBS). Their patient had optic atrophy secondary to unrelieved papilloedema with no light perception in the left and minimal light perception in the right eye. The background to Bonnet's syndrome and its putative explanation may therefore be of interest.

Figure 1: Charles Bonnet

Charles Bonnet (1720-93) (Figure 1) was a Swiss lawyer whose main recreations were as a naturalist and philosopher. In 1760 he described vivid, complex visual hallucinations in his psychologically normal 87-year-old grandfather, Charles Lullin,[1] who had had cataract operations on both eyes and was practically blind (Figure 2). Lullin described silent visions of men, women, birds, carriages, and buildings, which he fully realised were 'fictions' of his brain. Bonnet himself later underwent visual deterioration and experienced hallucinations typical of the syndrome named after him by de Morsier in 1936.[2] In this original paper he defined the Charles Bonnet syndrome:

"Dans les syndromes séniles avec lésions oculaires—le syndrome de Charles Bonnet—(les hallucinations visuelles) peuvent être isolées avec intégrité complète des autres fonctions cérébrales".

"In the senile syndromes with ocular lesions the syndrome of Charles Bonnet- (visual hallucinations) can be isolated with complete integrity from other cerebral functions."

He recognised that visual hallucinations occurred in a range of clinical conditions and his intention was to differentiate the Charles Bonnet cases from visual hallucinations associated with parietal lesions, peduncular lesions and chronic hallucinatory psychoses. He also commented that the ocular lesions that one generally finds among these hallucinating old men are not the cause of their hallucinations:

"Contrairement à la théorie soutenue par les oculistes les lésions oculaires qu'on trouve le plus souvent chez ces vieillards hallucinés ne sont pas la cause de ces hallucinations".

"Contrary to the theory supported by oculists, the ocular lesions that one generally finds among these hallucinated old men are not the cause of these hallucinations".

In his later 1967 review de Morsier, insisted that eye disease be excluded from the definition since it was not the most important aetiological factor; and emphasised instead the role of ageing on the cerebral visual pathways and the absence of a neuropsychiatric disorder:

"En 1938, j'ai proposé de désigner sous le nom de 'syndrome de Charles Bonnet' les hallucinations visuelles apparaissant chez les vieillards sans déficience mentale. Pour éviter toute confusion, il convient de conserver cette définition. Cette par erreur que quelques auteurs ont donné récemment 'syndrome Charles Bonnet' comme synonyme d'hallucinations chez des ophtalmophathes. Il n'existe pas de corrélation entre les hallucinations visuelles et les lésions des globes oculaires. Les hallucinations visuelles ne peuvent pas être expliquées par une 'privation' d'afférences visuelles. Elles sont toujours causées par une altération du cerveau".[3]

'In 1938, I tried to indicate under the name of "syndrome of Charles Bonnet" the visual hallucinations appearing among old men without mental deficiency. To avoid any confusion, it is convenient to preserve this definition. This is an error which some authors have recently applied to the "syndrome Charles Bonnet" as a synonym for hallucinations of the ophthalmopathies. There does not exist a correlation between the visual hallucinations and the lesions of the ocular spheres. The visual hallucinations cannot be explained by a `deprivation' of visual afferents. They are always caused by a disorder of the brain'.

de Morsier thus introduced an ambiguity. Charles Lullin and Bonnet himself both had eye disease, yet the CBS was not intended to describe this association.[4] As a result, some authors follow de Morsier and reserve the Charles Bonnet eponym as a purely phenomenological description (complex hallucinations in the psychologically normal) without specifying visual impairment[5,6] and describe eye disease and old age as common clinical associations rather than diagnostic prerequisites. Other authors use the eponym to refer to those patients with complex visual hallucinations associated with eye disease.[7,8] ffytche and Howard observed that at one extreme the term is used to describe:

1. All patients with complex visual hallucinations with preserved insight regardless of causal cerebral lesions, or visual impairment, while
2. for others the term is used to describe patients with complex visual hallucinations and eye disease. The second view is most generally accepted, with the proviso that often, there may be other operant factors.

CBS appears to fall within the generalisation that patients with eye disease may experience the same distortions of visual perception as do those with cerebral lesions,[9] and some normal subjects. One series reported screening 505 visually handicapped patients of whom 60 were found to meet proposed diagnostic criteria for CBS (generally, visual hallucinations without delusions or loss of insight).[10]

Patients have described seeing cartoon characters, flowers, hands rubbing each other, waterfalls and mountains, tigers, brilliantly coloured trees, street scenes, faces or life-size figures that they've never seen before often showing pleasant expressions. The underlying mechanism remains unclear but ffytche et al's fMRI study of Bonnet's syndrome show that phasic increases in activity within specialized visual cortex can underlie hallucinations of vivid colours and distorted faces.[11] Indeed increases in visual cortical activity probably explain a variety of visual phenomena caused by different aetiologies that share a loss of inhibitory input.

JMS Pearce MD, FRCP is an Emeritus Consultant Neurologist at the Hull Royal Infirmary. His interests are in Clinical Neurology and the History of Medicine.

Correspondence to:
JMS Pearce,
304 Beverley Road,
Anlaby,
East Yorks,
HU10 7BG, UK.
Email: jmsp@freenet.co.uk

Table 1: Inclusion criteria for the Charles Bonnet Syndrome after Teunisse et al.[4]

- At least one complex visual hallucination within the past 4 weeks;
- A period between the first and the last hallucination exceeding 4 weeks;
- Full or partial retention of insight into the unreal nature of the hallucinations;
- Absence of hallucinations in other sensory modalities;
- Absence of delusions.

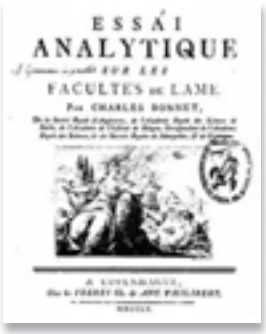


Figure 2: Title page: Essai Analytique Sur Des Faculte's De L'ame, 1760.

References

1. Bonnet C. *Essai analytique sure les faculte's de l'ame.* First Edition, Freres Cl. & Ant. Philibert Copenhagen, 1760.reprint Hildesheim, Georg Olms 1973.
2. de Morsier G. *Les automatismes visuels. (Hallucinations visuelles rétrochiasmatiques).* Schweiz Med Wschr 1936;66:700-3.
3. de Morsier G. *Le syndrome de Charles Bonnet: hallucinations visuelles des vieillards sans deficience mentale.* Annls Med Psychol 1967;125:677-702.
4. ffytche DH, Howard RJ. *The perceptual consequences of visual loss: 'positive' pathologies of vision.* Brain. 1999;122(Pt7):1247-60.
5. Damas-Mora J, Skelton-Robinson M, Jenner FA. *The Charles Bonnet syndrome in perspective.* Psychol Med. 1982;12:251-61.
6. Gold K, Rabins PV. *Isolated visual hallucinations and the Charles Bonnet syndrome: a review of the literature and presentation of six cases.* Compr Psychiatry. 1989;30:90-8.
7. MenonGJ. *Complex Visual Hallucinations in the Visually Impaired.* Arch Ophthalmol. 2005;123:349-55.
8. Podoll K, Osterheider M, Noth J. *The Charles Bonnet syndrome [in German].* Fortschr Neurol Psychiatr. 1989;57:43-60.
9. Critchley M. *Types of visual perseveration: `paliopsia' and `illusory visual spread'.* Brain 1951;74:267-99.
10. *Teunisse RJ, Cruysberg JR, Hoefnagels WH, VerbeekAL, Zitman FG. Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome.* The Lancet 1996;347:794-7.
11. ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S. *The anatomy of conscious vision: an fMRI study of visual hallucinations.* Nat Neurosci 1998;1:738-4.

Fitness to Ride – Horse Racing in Great Britain

Dr Michael Turner is the Chief Medical Adviser (CMA) to the British Horseracing Authority (BHA), a post he has held since 1993. The BHA has been the regulator of horse racing in Great Britain since 2007, a role performed by the Jockey Club for the previous 250 years. He is also Medical Adviser to the Lawn Tennis Association and is a former CMA to British Snowsports and Director of Medical Services at the British Olympic Association. He has published widely on equestrian sporting injuries and has a particular interest in concussion.

Correspondence to:
Dr Michael Turner,
Fax. 020-7189-3836
Email. mturner@
britishhorseracing.com

Horse racing is an immensely popular global sport with television audiences of over 100 million for major event – Melbourne Cup, Kentucky Derby. Racing takes place on 60 racecourses in England, Scotland and Wales and there are approximately 1475 race meetings annually with total attendance figures of over 5 million spectators.

Racing is broadly divided into flat and jump racing and involves both amateur and professional riders. All riders are over 16 and all types of racing take place over a full 12 month season, apart from Point to Point (PtoP) racing. PtoP is jump racing that is restricted to amateurs and has a limited season (November to June).

There are approximately 110,000 rides a year (60,000 flat, 35,000 jump and 12,000 Point to Point) and 1800 jockeys are licensed annually by the BHA (250 flat, 200 jump, 450 amateurs and 900 PtoP amateurs).

Over the period 1993-2007, there have been over 20,000 fixtures, 1.3 million rides, 53,000 falls, 10,250 injuries and 1,275 concussions in Great Britain, details of which are already in the published literature.[1,2,3]

Horses travel at 20-40mph, the jockey is seated in a saddle perched two metres above the ground and a ride may last anything from 40 seconds (flat) to 6 minutes (jump).

Incidence and type of injury

Amateur jockeys fall every 7.9 rides, Jump jockeys fall every 15.8 rides and Flat jockeys fall every 211 rides on turf (every 258 rides on All-Weather tracks). It is therefore not surprising that horse racing has some of the highest rates of injury seen in any sport, including the highest rates of concussion and fatal accidents in the published literature. Concussion rates are in fact six times greater than in Australian Rules Football – the sport with the closest incidence of concussion.

Soft tissue injuries account for 75-80% of all injuries, fractures 10-18%, dislocations 1-4% and concussion 8% (professional racing) - 18% (amateur racing).

Regulations

Horse racing has detailed regulations covering all aspects of a jockeys' fitness to hold a license, clearance to return to race riding following an accident, and the minimum medical provisions required on every racecourse on every raceday. These are published on the BHA website -

Standards of Medical Fitness to Ride
http://www.britishhorseracing.com/inside_horseracing/about/whatwedo/medical/medical.asp

Provision of medical services on racecourses – BHA General Instruction 11
http://www.britishhorseracing.com/inside_horseracing/pdf/hragi_11.pdf

Prohibited substances and testing of jockeys
http://www.britishhorseracing.com/inside_horseracing/about/whatwedo/medical/testing-banned-bkt.pdf

Fitness to Ride regulations
When applying for an initial licence, every rider must reach the minimum medical standard of fitness to ride. The same standard applies to all amateur and professional jockeys and some specified conditions warrant exclusion – epilepsy, anti-coagulant therapy, deafness, monocular vision, insulin-dependent diabetes etc.

Jockeys are required to notify the BHA Medical Department immediately if they suffer any illness or injury during the 12 months that the licence is valid. All jockeys are required to renew their licences annually and are required to complete a Health Declaration with details of all injuries and illnesses suffered since the last application. In addition, all jockeys are required to have a full medical examination carried out by their own GP every five years.

When riders reach a designated age threshold (over 37 jump, over 45 flat, over 55 amateur), they are also required to have an annual medical examination by the BHA CMA (to include blood profile, ECG and Exercise Stress Test if warranted).

Protection equipment

The Rules of Racing require all riders to wear helmets and body protectors when race riding and all protective equipment must meet the current European Standard – EN 1384.1996 (helmets) and EN 13158.2000 (body protectors). Helmets cost around £120 each and are designed as 'single impact protectors'- so should be discarded after every head injury or concussion. Body protectors are only designed to mitigate rib fracture (not injuries to the spine) and cost around £150.

Injury monitoring and recording

On every raceday, a minimum of two trauma trained doctors are required to be on duty (Racecourse Medical Officers – RMOs). When a jockey falls, a doctor or paramedic must attend the faller rider within 60 seconds. Before riding again, the jockey must be examined by an RMO and a decision made as to his/her fitness to continue riding that day. All injuries must be recorded on a standardised form (MRB3) and reported to the BHA Medical Department at the end of racing. These are referred to as "Red Entries" and these data are currently stored on a central computer database within racing (Weatherbys). This system will shortly be replaced by a customised injury management system (Presagia Sports – Injury Zone). In addition, amateur riders carry a "Medical Record Book" (MRB) with details of all injuries incurred during racing – a medical passport. For amateurs, the RMO will record the Red Entry in the MRB as well as recording it on the MRB3 Form.

All jockeys who are unable to ride, for whatever reason, are recorded on a "Red Entry List". This list is updated each evening and is available on every racecourse before racing starts. Any jockey whose name appears on the Red Entry List must be medically cleared by the BHA CMA and examined by a RMO before they are allowed to return to race riding.

For example, a jockey who suffers a fracture-dislocation of the shoulder will be sent directly to hospital in an ambulance and his name entered on the Red Entry List. When he has completed treatment, his specialist will be required to send a detailed report to the BHA CMA confirming that the condition is resolved and that the jockey can return to race riding. The BHA CMA may request additional information or examine the jockey himself but, more usually, the BHA CMA will accept the specialist recommendation and allow the jockey to return to a racecourse for examination by an RMO. Before racing starts, the RMO is required to examine the injured jockey and decide if the rider is in fact fit to race ride. At that stage, the RMO will either clear the Red Entry (allowing the jockey to ride) or, refer the jockey back to the BHA CMA for further evaluation.

Jockeys who are subject to a medical suspension (Red Entry) are uninsured and cannot ride in GB or any other country until cleared by the BHA CMA. Medical standards of fitness to ride apply across all racing authorities (Article 27 of the International Agreement) and some injuries are inevitably career ending.[4,5,6,7]

Concussion management

Prior to 2004, the Jockey Club operated a fixed period of suspension (related to loss of consciousness – LOC) for any jockey who suffered concussion:

Mild –	no LOC – jockey suspended for 2 clear days
Moderate –	LOC of less than 60 seconds – jockey suspended for 6 clear days
Severe –	LOC of over 60 seconds – jockey suspended for 20 clear days

In 2004, the Jockey Club/BHA introduced a standardised concussion management system and analysis of some 350 concussions that occurred in the 4.5 year period, 1st Jan 2004 – 30th June 2008, will be published shortly. The total budget for the BHA Concussion program is approximately £80,000 pa.

The current BHA Concussion protocol has three elements -

1. Neuro-Psychological (NP) testing
This takes place at one of 12 regional centres established by the BHA. These centres are located in private (independent) hospitals or GP surgeries and a trained nurse at each location will carry out the NP testing on behalf of the BHA. The jockey is required to complete a computerised test (CogSport) and a series of pen and paper tests (Colour trails, STROOP, Symbol-digit, SCOLP, digit span) – the whole process takes about 60 minutes to complete. The various tests are then evaluated by one of 4 Clinical Neuro-Psychologists retained by the BHA.

2. Standard Assessment of Concussion (BHA AC). Whenever a jockey suffers a concussion, the doctor in attendance at the racecourse will carry out a standardised concussion assessment as mandated by the BHA. This involves a set of screening questions and a more detailed neurological evaluation for those riders who fail to answer the screening questions correctly. In every case, the doctor will be required to make a definitive diagnosis in regard to concussion. Is this rider suffering from concussion – YES/NO?

3. Post-concussion evaluation (fitness to return to race riding). Any rider who is diagnosed as having concussion (as per 2/ above) will be required to undergo a two part evaluation before being allowed to return to race riding. This evaluation will normally take place no earlier than six clear days after the concussive incident:

a) Repeat NP testing (as for 1/ above) with report from Neuro-Psychologist.
b) Examination by a Consultant Neurologist (or Neurosurgeon). This consultation takes place at the same Regional Centre as the NP testing.

The reports from both these examinations are sent to the BHA CMA who is then responsible for deciding if the rider can safely be allowed back to race riding, or if a further period of rest is required. If the NP tests have not returned to baseline levels, the rider will normally be suspended for a further 14 days after which repeat post-concussion evaluation will take place (NP testing +/- consultant review). This process will be repeated until it is deemed safe for the rider to return to race riding.

The arrangements for baseline screening vary for the different types of jockey but the BHA AC and post-concussion review are identical for all jockeys (see Stages 1 and 2 above).

Professional jockeys
Neuro-Psychological testing - annual baseline

Amateur jockeys
Neuro-Psychological testing - baseline before first license is issued and repeat baseline every 5 years (or at the start of the season after any concussion)

Point-to Point Riders (who do not hold an Amateur Licence – see above)
Neuro-Psychological testing – no baseline required but NP testing is available to riders on a voluntary basis (cost to be paid by the rider)

Head height for a jockey is approximately three metres above the ground and a fall from over two metres warrants specific medical management under the NICE Guidelines on Head injuries (June 2007).[8]

References

1. Turner M, McCrory P, Halley W. *Injuries in professional horse racing in Great Britain and the Republic of Ireland during 1992–200.* Br. J. Sports Med. Dec 2002;36:403-9.
2. McCrory P, Turner M, LeMasson B, Bodere C, Allemandou A. *An analysis of injuries resulting from professional horse racing in France during 1991–2001: a comparison with injuries resulting from professional horse racing in Great Britain during 1992–2001.* Br. J. Sports Med. Jul 2006;40:614-8.
3. Balendra G, Turner M, McCrory P, Halley W. *Injuries in amateur horse racing (point to point racing) in Great Britain and Ireland during 1993–2006.* Br. J. Sports Med. Mar 2007;41:162-6.
4. Balendra G, Turner M, McCrory P. *Career-ending injuries to professional jockeys in British horse racing (1991–2005).* Br. J. Sports Med. Jan 2008;42:22-4.
5. Turner M, Balendra G, McCrory P. *Payments to Injured Professional Jockeys in British Horse Racing (1996-2006).* Br. J. Sports Med. Apr 2008; doi:10.1136/bjsm.2007.040337
6. Patel J, Turner M, Birch R, McCrory P. *Rupture of the axillary (circumflex) nerve and artery in a champion jockey.* Br. J. Sports Med. Oct 2001;35:361-2.
7. McCrory P, Turner M, Murray J. *A punch drunk jockey?* Br. J. Sports Med. Jun 2004;38:e3.
8. *NICE Guidelines on Head Injury Triage, assessment, investigation and early management of head injury in infants, children and adults.* September 2007.CG56 - http://www.nice.org.uk/CG56.

Computed Tomography in Neurology

Computed tomography (CT) of the head was first used in clinical practice at the Atkinson Morley's Hospital, London in 1972. On the earliest equipment, images were low resolution and tediously slow to acquire involving several hours of acquisition and processing time. Now, high resolution images of the brain can be obtained in a few seconds. Speed is a great strength of modern CT making it ideal for ill and poorly co-operative patients. Rapid data acquisition is exploited in contrast enhanced angiography and perfusion techniques, although these will not be discussed in detail in this article. CT is still the best method available to detect bony abnormalities and acute blood products. For these reasons, CT remains at the forefront of neuroradiology despite the remarkable advances in other imaging technologies.

Basic physics

X-ray images are formed by interactions of X-ray photons with matter. As photons pass through objects, they interact primarily with electrons. The photon may be completely absorbed releasing an electron from an atom (photoelectric effect). More usually, the photon is not fully absorbed but part of its energy is used to move an electron into a higher energy orbital (Compton effect). The photon emerges from this interaction with reduced energy and is slightly deflected from its original course. These effects on photons generate image contrast because tissues attenuate photons to differing extents depending on their electron density. The electron density of tissue components is quantified using CT and thus reliably differentiated.

CT uses data from a bank of detectors which are irradiated by a tube rotated around the patient. In the first generations of CT equipment, data was acquired slice by slice. A significant advance came with the development of slip ring technology which allows continuous gantry rotation around the patient and thus data acquisition from a volume of tissue (so called helical or spiral CT). This increases the speed of imaging and provides the information required for 3D reconstructions with no gaps between slices. The latest technology has taken this idea a step further, using a large bank of detectors capable of acquiring up to 320 slices in a single gantry rotation lasting less than a second (so called multislice, multidetector or volume CT).

Processing the data from detectors is a complicated process requiring powerful computers. Images are constructed using algorithms which not only localise anatomical structures but minimise artefacts. There are different algorithms available which demonstrate bone, brain and soft tissues optimally.

Approach to neurological CT

1. Anatomical localisation of lesions

One of the most difficult and important steps in trying to work out the nature of a lesion is to decide whether a mass arises inside the brain parenchyma or outside, usually from the meningeal coverings. A lesion within the brain parenchyma is termed intra-axial and one outside is extra-axial. The shape of a mass and its effect on neighbouring structures (such as displacement of brain and bone remodelling) are helpful in making this distinction. Parenchymal lesions can be usefully divided into those involving grey or white matter. For example, many tumours arise in white matter, whereas ischaemia typically affects grey matter, causing loss of grey-white differentiation.

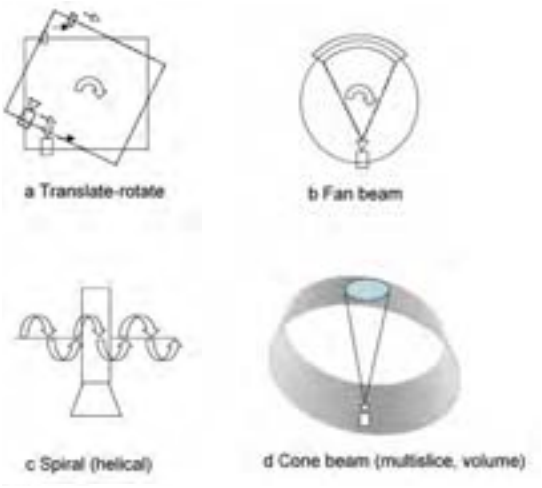


Figure 1: Generations of CT scanners.
A. Initial CT equipment used linear motion of tube and detector followed by rotation of the gantry by a few degrees. This process had to be repeated up to 30 times, resulting in acquisition times of 30-60 mins per slice.
B. Later generations of CT scanners avoided the need for linear motion by using a fan beam. This reduced acquisition times to less than 1 minute per slice.
C. Spiral or helical CT allows continuous gantry rotation while the patient is moved through the scanner. This further increased acquisition speed.
D. Multislice equipment uses banks of detectors to acquire multiple slices (typically 64) per rotation so that the whole brain can be imaged in a few seconds.

Table 1: CT terminology (see Figure 1)	
Helical/spiral/volumetric CT	Data acquisition occurs as the patient moves through the gantry generating a volume dataset. This can be post-processed into images of different slice thickness in any plane.
Multislice/multidetector/multirow CT	Multiple rows of detectors (typically 16, 64 or 128 rows of 0.5mm thickness) are installed in the gantry so that many imaging slices can be obtained with one rotation.
Post-processing	Image manipulation performed after data has been acquired.
High resolution CT	Thin section images viewed after processing with an edge-enhancing algorithm. This allows detection of very small structures (eg bone in the middle ear down to 0.5 mm or less in thickness). This technique only works in tissues where there is high intrinsic contrast (eg bone or lung). When applied to soft tissues the algorithm provides a very grainy appearance.
Image contrast/Contrast resolution	The difference in density between tissues determines how easily they can be distinguished using imaging. The areas of the body where there is greatest contrast between pathology and normal tissue on CT are the lungs and bones. In brain, white matter and grey matter can be differentiated with Hounsfield Unit (HU) of 20 and 30 respectively (see Figure 10).
Algorithm/Kernel	Computerised reconstruction of data which optimises images. This ranges from image smoothing (for soft tissue) to edge enhancement (for bone and lung). Algorithms are used to suppress artefacts caused for example by beam hardening.

Dr Justin Cross trained in neuroradiology at Addenbrooke's Hospital, Cambridge UK and at the University of Toronto, Canada. He has a special interest in paediatric neuroradiology and has published articles on the measurement of cerebral tumour volume, carotid imaging and the use of spectroscopy in clinical practice.

Correspondence to:
Dr Justin Cross,
Department of Radiology,
Box 218,
Addenbrooke's Hospital,
Hills Road,
Cambridge CB2 0QQ, UK.

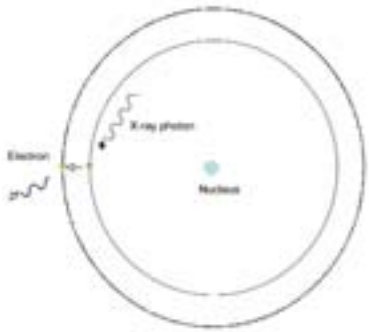


Figure 2: X-ray photons of suitable energy interact with electrons, either releasing them from the atom (ionisation) or pushing them into a higher energy orbital. In the process, the photon may be completely absorbed, or reduced in energy. The interaction may also cause deflection of the photon (see Table 2).

Table 2: Physics/techniques (see Figure 2)	
Compton and photoelectric effects	These describe the interaction of X-ray photons with physical matter. In the photoelectric effect, a photon of suitable energy is completely absorbed, releasing an electron from its orbit around the nucleus. In this process, positively charged ions are produced. In Compton interactions, the X-ray photon is not completely absorbed, but deposits some of its energy, displacing but not removing an electron from an atom. The X-ray photon's course is deflected and its energy is reduced. The deflection of the photon is a source for the loss of sharpness in the CT image.

a. Skull/scalp (Figure 3)
Lytic or sclerotic metastatic bone lesions may be seen on CT. Fractures are often better seen on plain films than CT.

b. Dura mater (Figure 4)
Most normal dura mater (apart from the falx and tentorium) is not seen on CT as it is applied to the skull.

c. Arachnoid mater/subarachnoid space (Figure 5)
CSF spaces are easily compressed by space occupying lesions or by brain swelling. In hydrocephalus, the ventricles are typically large with effacement of cerebral sulci. In young people the sulci are normally small and this can be misinterpreted as brain swelling. Enlargement of the sulci usually indicates volume loss, either focal (eg related to an infarct) or diffuse (usually related to atrophy/neurodegeneration). Increased density in the sulci typically indicates subarachnoid haemorrhage.

d. Grey matter (Figure 6)
Infarcts typically involve grey matter but contusions and low grade tumours may be seen here.

e. White matter (Figure 7)
This is a typical site for high grade gliomas. Metastases and abscesses are often seen near the grey-white junction because of the high blood flow here, and the size of the vessels in which tumour cells and bacteria can lodge. Oedema also involves white matter (Figure 11).

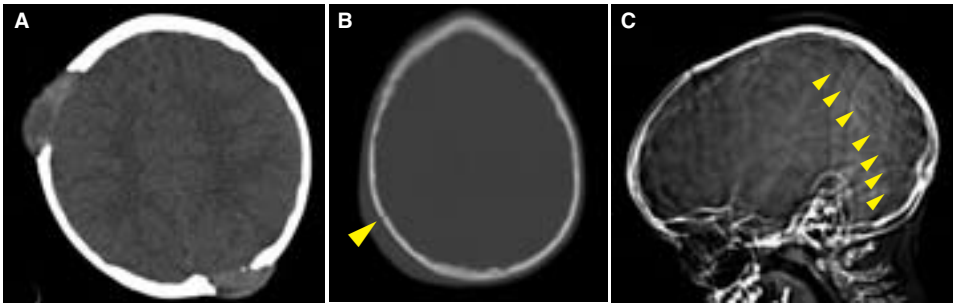


Figure 3: Scalp/skull lesions.
A. Skull lesions from Langerhan's cell histiocytosis. B and C. Skull fracture. Note the full extent of the fracture is often better appreciated on plain film (arrowheads indicate fracture).

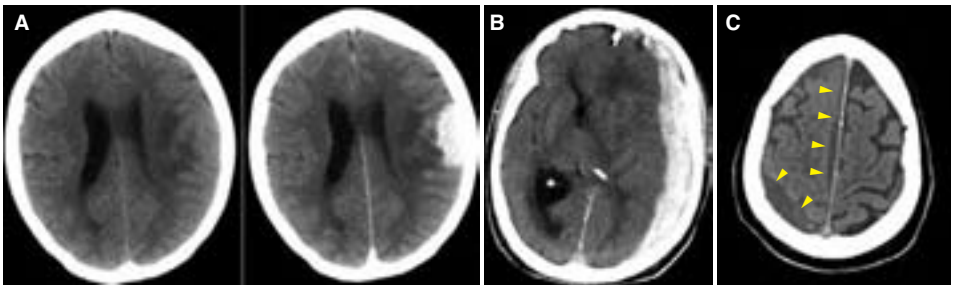


Figure 4: Dura mater. A. Images with and without contrast medium. Meningioma with a wide base on the convexity dura. B. Subdural haematoma extending along the dural surface of the hemisphere. C. Post contrast CT image with a subdural empyema indicated by arrowheads. Note compression of the subarachnoid spaces.

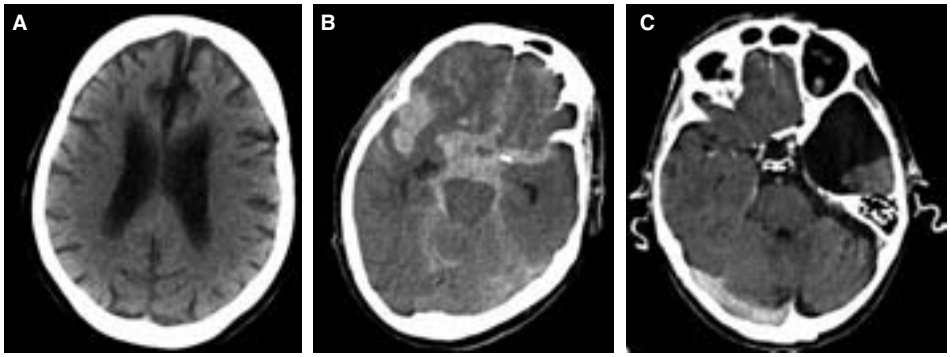
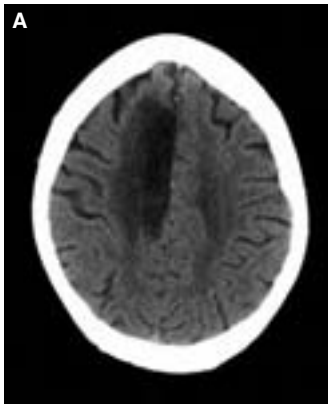


Figure 5: Arachnoid mater/ subarachnoid space.
A. Prominent subarachnoid spaces due to atrophy. B. Subarachnoid haemorrhage. C. Arachnoid cyst.



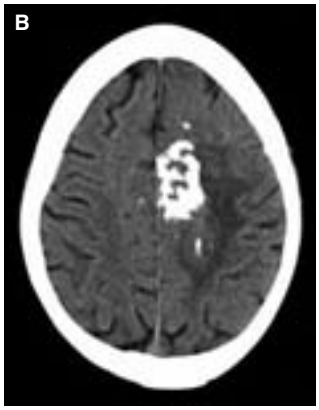
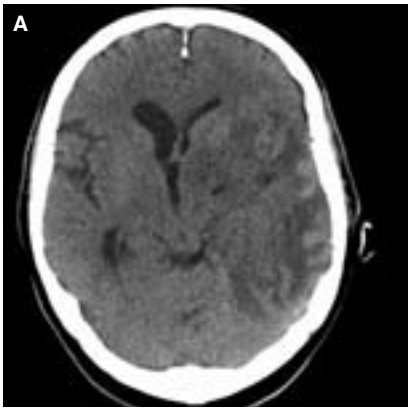


Figure 6: Grey matter.
A. Established cortical infarct in the anterior cerebral artery territory.
B. Calcified low grade oligodendroglioma.



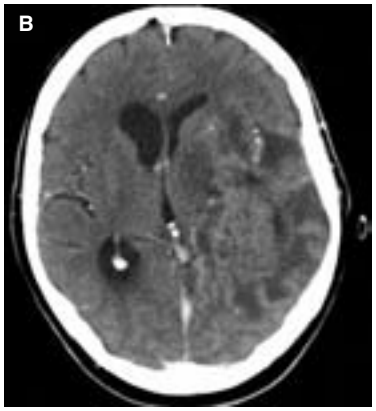
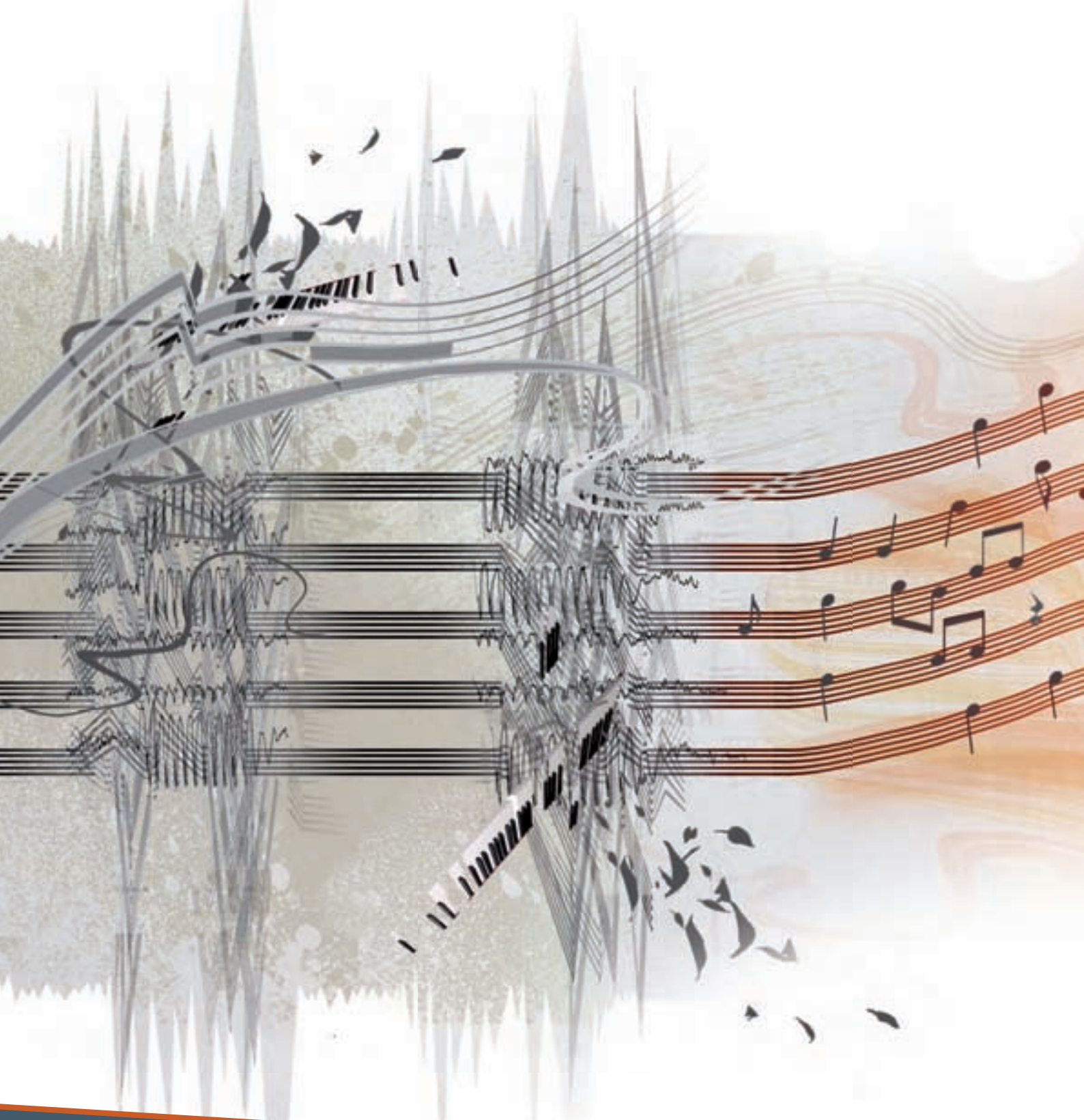
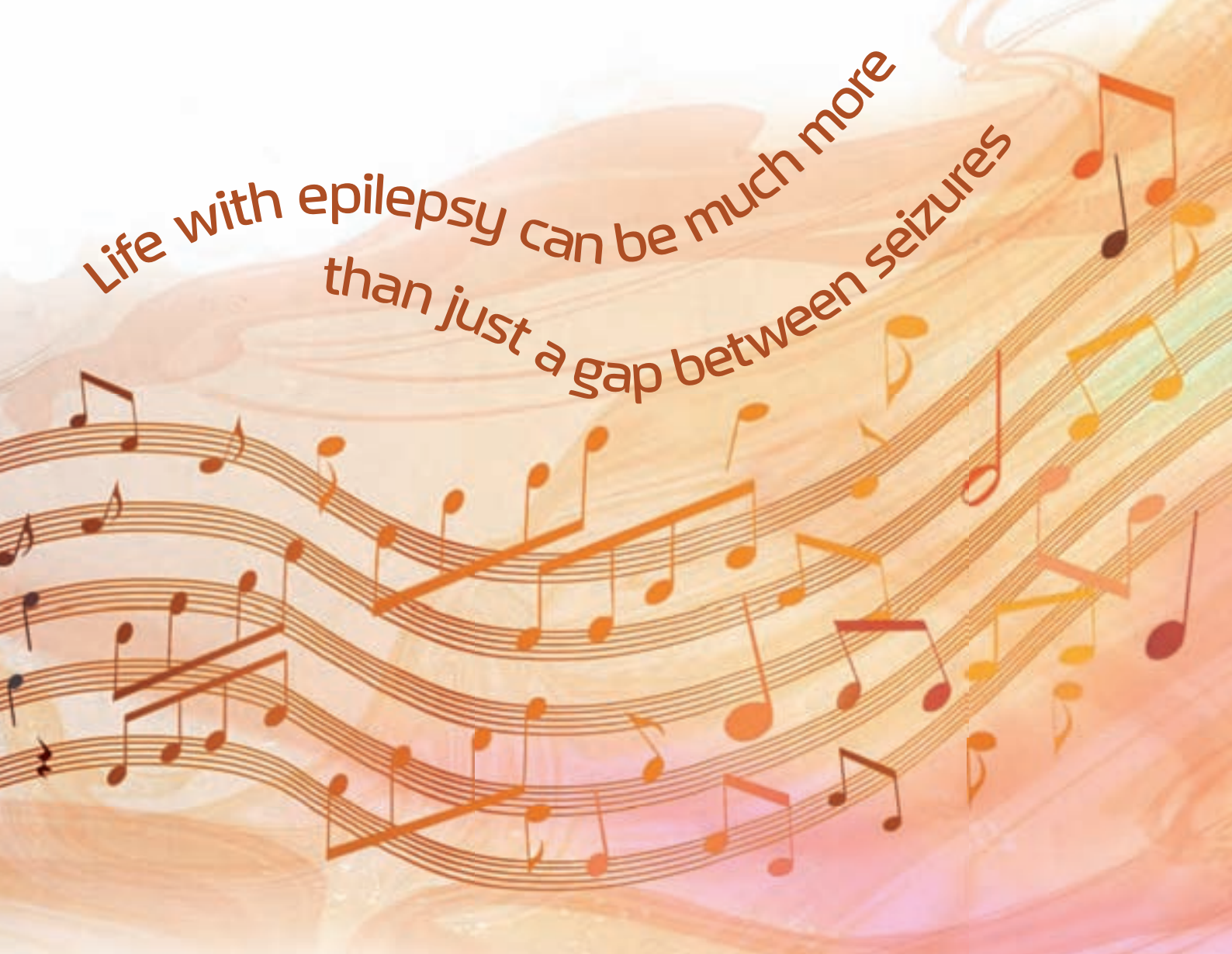


Figure 7: White matter.
A and B. High grade glioma with vasogenic oedema (A before and B after contrast medium).
See Figure 11 for description of patterns of oedema.



ABBREVIATED PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing). **VIMPAT 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets VIMPAT 15 mg/ml syrup VIMPAT 10 mg/ml solution for infusion Active Ingredient**: *Tablets:* lacosamide 50 mg, 100 mg, 150 mg and 200 mg film-coated tablets. *Syrup:* lacosamide 15 mg/ml. *Solution for infusion:* lacosamide 10 mg/ml. **Therapeutic Indications**: VIMPAT is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older. **Dosage and Administration**: *Adults and adolescents from 16 years:* Recommended starting dose is 50 mg twice a day which should be increased to an initial therapeutic dose of 100 mg twice a day after 1 week. Maximum daily dose of 400 mg (in two 200 mg doses). For *solution for infusion*: Infused over a period of 15 to 60 minutes twice daily. Can be administered i.v. without further dilution. *Elderly:* No dose reduction necessary. Age associated decreased renal clearance with an increase in AUC levels should be considered. *Paediatric patients:* Not recommended. *Patients with renal impairment*: No dose adjustment necessary in mild and moderate renal impairment. Dose adjustment is recommended in SPC for patients with severe renal impairment and patients with end-stage renal disease. Dose titration should be performed with caution. *Patients with hepatic impairment:* No dose adjustment needed in mild to moderate impairment. In accordance with current clinical practice, if VIMPAT has to be discontinued, it is recommended this be done gradually (e.g. taper the daily dose by 200 mg/week). **Contraindications, Warnings etc**.: *Contraindications*: Hypersensitivity to lacosamide or to any of the excipients. Known second- or third-degree atrioventricular block. In addition for *tablets*, hypersensitivity to peanuts or soya. *Precautions*: Lacosamide has been associated with dizziness. Use with caution in patients with known conduction problems, severe cardiac disease or in elderly. Excipients in the *syrup* may cause allergic reactions (possibly delayed), should not be taken by those with fructose intolerance and may be harmful to patients with phenylketonuria. *Interactions*: Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically



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

VIMPAT®
lacosamide

Confidence of additional seizure control

relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. *Pregnancy and Lactation*: Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. *Driving etc.*: Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of VIMPAT on their ability to perform such activities. **Adverse Effects:** *Very common (≥10%)*: Dizziness, headache, diplopia, nausea. *Common (between 1%-10%):* Depression, balance disorder, abnormal coordination, memory impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions**: *Tablets:* None. *Syrup:* Do not store above 30°C. Use within 4 weeks of first opening. *Solution for infusion:* Do not store above 25°C. Use immediately. **Legal Category**: POM. **Product Licence Numbers**: 50 mg x 14 tabs: EU/1/08/470/001; 100 mg x 14 tabs: EU/1/08/470/004; 100 mg x 56 tabs: EU/1/08/470/005; 150 mg x 14 tabs: EU/1/08/470/007; 150 mg x 56 tabs: EU/1/08/470/008; 200 mg x 56 tabs: EU/1/08/470/011; Syrup (15 mg/ml) x 200 ml: EU/1/08/470/014; Solution for Infusion (10 mg/ml) x 20 ml: EU/1/08/470/016. **NHS Cost**: 50 mg x 14 tabs: £9.01; 100 mg x 14 tabs: £18.02; 100 mg x 56 tabs: £72.08; 150 mg x 14 tabs: £27.03; 150 mg x 56 tabs: £108.12; 200 mg x 56 tabs: £144.16; Syrup (15 mg/ml) x 200 ml: £38.61; Solution for Infusion (10 mg/ml) x 20 ml: £29.70. **Name and Address of PL Holder**: UCB Pharma S.A., Allee de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformation@ucb-group.com. **Date of Revision:** September 2008. VIMPAT is a registered trade name. **References:** 1. VIMPAT® Summary of Product Characteristics, September 2008. 2. Beyreuther BK *et al. CNS Drug Rev* 2007; **13**(1): 21–42. 3. UCB Data on file. **Date of preparation:** September 2008. 08VPE0188

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

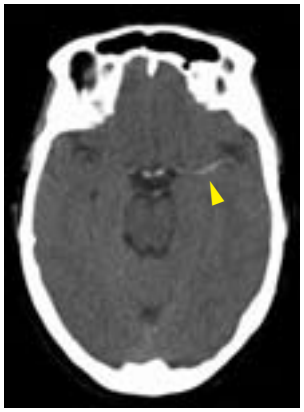


Figure 8: Vessels.
Dense middle cerebral artery following recent occlusion (arrowhead).

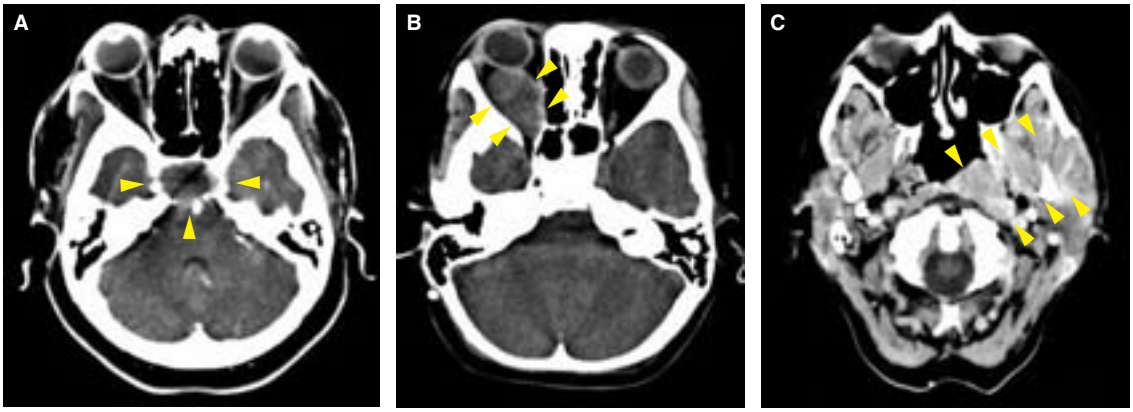


Figure 9: Blindspots.
A. The sella is enlarged by a pituitary adenoma (arrowheads). B. Orbital mass (arrowheads). C. Lymphoma involving nasopharynx and infratemporal fossa (arrowheads).

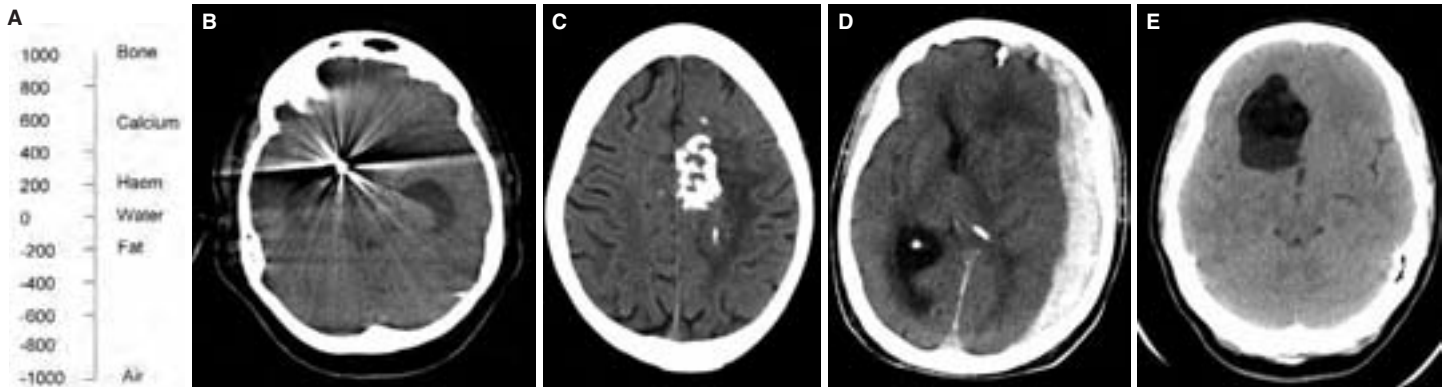


Figure 10: Density of lesions.
A. Hounsfield Units (HU). Each tissue type has a specific electron density which can be quantified into attenuation coefficients or Hounsfield Units. B. Coil inserted in an intracranial aneurysm is of very high density and causes artefact (HU>1000) because of the attenuation of the x-ray beam. C. Calcification in a low grade glioma (HU=500). D. Recent haemorrhage in a subdural collection (HU=200). E. Dermoid containing fat (HU=-200).

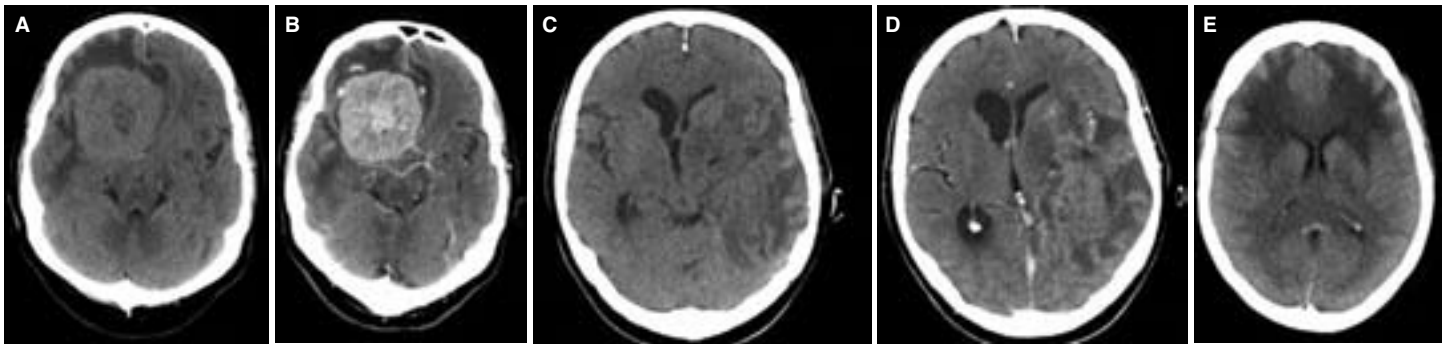


Figure 11: Outline/ patterns of oedema.
A and B. Pre- and post-contrast imaging. Meningioma showing a well defined margin. C and D. Pre- and post-contrast imaging. Glioma showing ill defined margins. E. Vasogenic oedema involving white matter only, in a case of olfactory groove meningioma (tumour not shown).

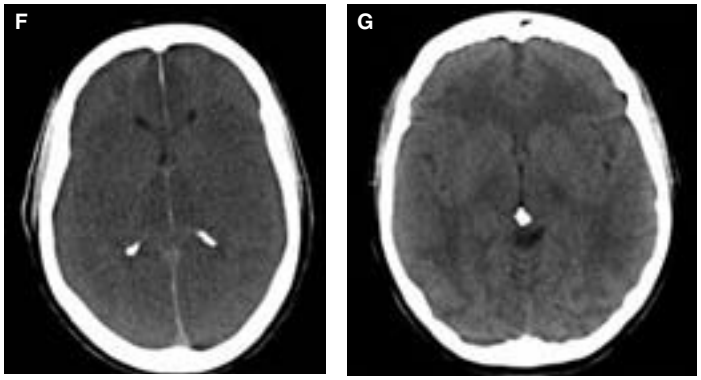


Figure 11
F. Cytotoxic oedema involving grey and white matter in diffuse cortical necrosis following cardiac arrest. G. Normal brain for comparison

f. Vessels (Figure 8)

Focal increased density in a vessel may indicate recent thrombosis. Aneurysms are rarely identified on unenhanced CT but may be seen following contrast enhancement.

g. Blindspots (Figure 9)

Extracranial soft tissues may show pathology which is incidental to the symptoms for which imaging was performed. The sella, skull base and orbits are frequent blind spots.

2. Characterising lesions

a. Density (Figure 10)

The CT density of different tissue types can be predicted (Fig 10a-e). In practice, tumour types cannot be precisely differentiated from density alone, but certain tumours (meningioma, lymphoma, medulloblastoma) tend to be higher density than others (glioma). Detection of calcium and blood is often easier on CT than MRI.

Table 3: Artefacts (see Figure 14)	
Beam hardening	As the beam of Xray photons pass through dense bone, lower energy photons are absorbed resulting in a beam with higher average energy. These photons traverse soft tissue adjacent to the bone with less attenuation than on other slices and the soft tissue appears spuriously low in density.
Partial volume	Partial volume effects occur when the slice of data acquisition includes tissues of different density. For example a slice containing half ventricle and half brain will be displayed as having a density intermediate between the two.
Motion	Artefact from movement is usually easily recognised, although with more complex methods of CT data acquisition, motion has less predictable effects on the image.
Back projection	The CT image is constructed by computerised back projection of data. This would produce a perfect image if an infinite number of back projections were used. Star like radial lines may be seen around dense structures because of imperfect back projection.
Faulty detectors	If one or more detectors are not functioning, a variety of artefacts may be produced, the most common of which is a ring near the centre of the image.

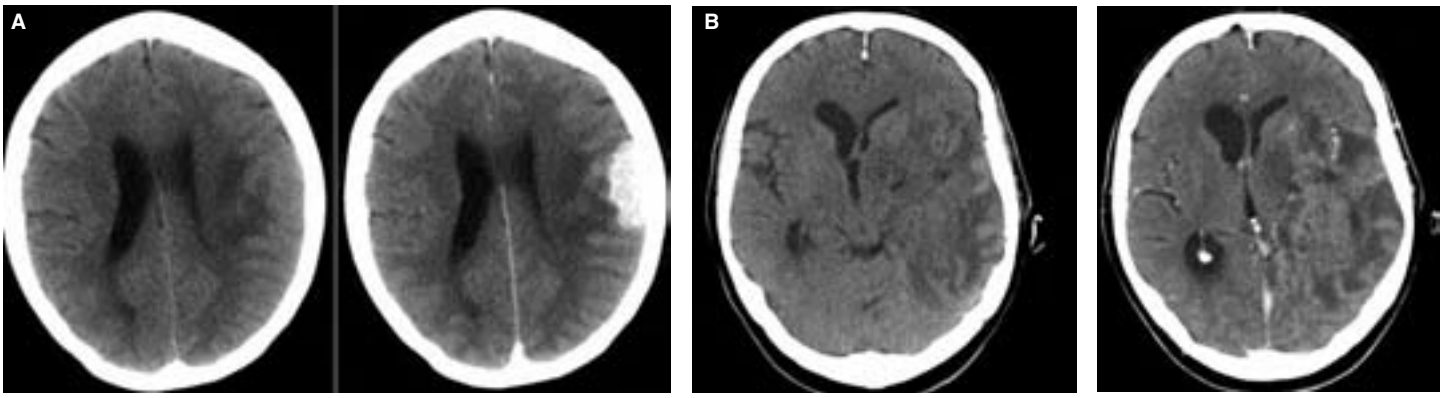


Figure 12: Patterns of contrast enhancement.
A. Image before and after IV contrast medium. Homogeneous enhancement in a meningioma. B. Image before and after iv contrast medium. Heterogeneous enhancement in a glioma.

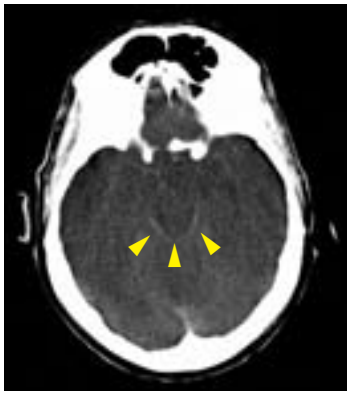


Figure 13: Mass effect.
Diffusely swollen brain with effacement of perimesencephalic cisterns indicating trans-tentorial herniation (arrowheads).

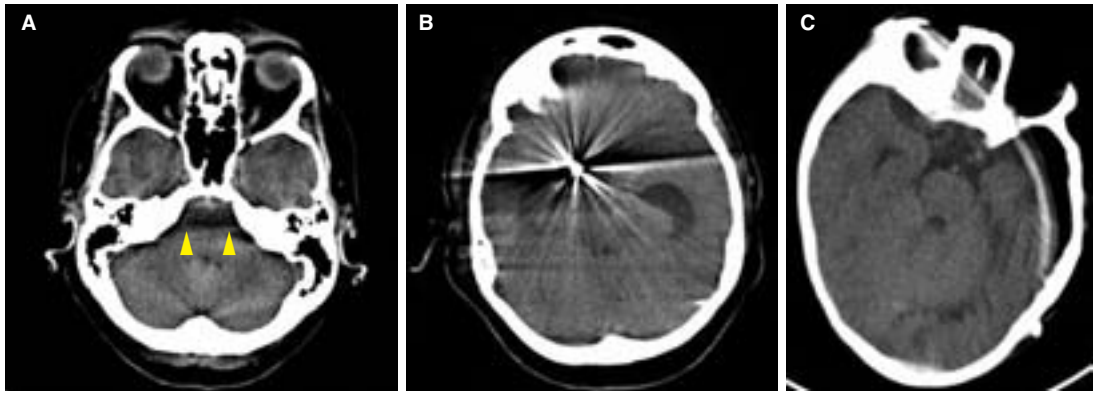


Figure 14: Artefacts (see Table 3).
A. Beam hardening causing apparent low density in the brainstem (arrowheads).
B. Back projection or star artefact around a dense metal coil.
C. Motion artefact on multislice CT can result in an unusual appearance with distortion of only part of the image.

b. Outline/ patterns of oedema (Figure 11)
Many benign tumours have well defined margins whereas aggressive tumours and inflammatory processes tend to be ill-defined. This does not apply universally and some rapidly growing tumours may appear well-defined.

Vasogenic oedema is caused by disruption of the blood brain barrier around inflammatory, neoplastic or ischaemic lesions. This is usually confined to white matter. Cytotoxic oedema is caused by ischaemia and involves grey and white matter.

c. Contrast enhancement (Figure 12)
Contrast enhancement is caused by a combination of increased vascularity and disruption of the blood brain barrier. Patterns of enhancement clarifies the extent of abnormality and can help differentiate disease processes.

d. Mass effect (Figure 13)
Recognising the consequences of mass effect is important as shift between intracranial compartments can result in rapid clinical deterioration because of pressure on vital structures.

3. Recognising artefacts (Figure 14)
The appearance of artefacts is learned through experience but a few examples are provided in Figure 14.

Conclusion

Neurological CT continues to develop rapidly with new technology becoming available almost every year. CT is not only the first line neurological imaging investigation, but also provides excellent diagnostic information which is complementary to other techniques such as MRI. More advanced applications of CT such as angiographic imaging and quantification of perfusion have not been covered in this article, but are becoming more widely used in clinical practice.

References
1. Smirniotopoulos JG, Murphy FM, Rushing EJ et al. *Patterns of contrast enhancement in the brain and meninges.* Radiographics 2007;27: 525-51.
2. Osborn AG, Blaser S, Salzman K et al. *Diagnostic Imaging: Brain.* Amirsys 2004.

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

Encephalitis, a guide

Published by: The Encephalitis Society
Price: £10 + postage/packaging
ISBN: 780955218033

'Encephalitis, a guide' comes in an interesting format. Slightly reduced A4 size, turned lengthways to open on strong spiral rings and holding a DVD in a pocket inside the end cover immediately says that this is a book production out of the ordinary. The pages open up easily, displaying two pages at a time and the dividers, well known to all with bulging ring folders, invite further exploration. Certainly a lot of time and trouble has been taken with the design. There are 6 sections. The style is clear, headings and paragraphs, highlights and encapsulated 'pearls of wisdom' appear with the same even editorial style. No obvious multi-author text here!

Section 1 – 'Encephalitis the Illness'
Section 2 – 'The Effects of Encephalitis'
Section 3 – 'Specialists and Services'
Section 4 – 'Returning to Normal Life'
Section 5 – 'Further Reading'

The factual presentation of the book is softened by the very personal approach of the DVD starring Martin Kemp, Patron to the Encephalitis Society, patients and families whilst not holding back on medical detail good or bad. The DVD ends with the place and purpose of the Encephalitis Society.

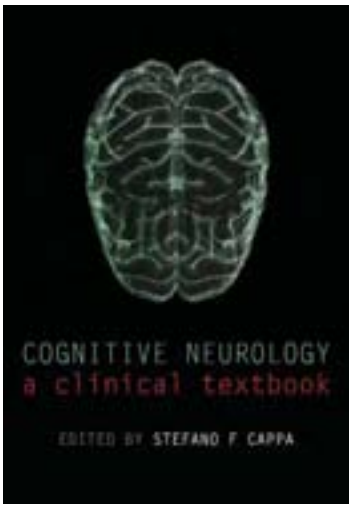
The book itself will find a place in every medical library. Professionals will be able to read it quickly. Patients and their families will read and re-read the book. So who is the real target audience?

There is a timely reminder for the professionals in Section 6 – 'pathways through a Medico-Legal Investigation' in other words 'how to start a medico-legal investigation if in the rare cases where recovery is compromised by poor medical care there is a legal entitlement to financial compensation'.

So the book is for families of Encephalitis sufferers from the Encephalitis Society who clearly mean business! If it makes us, the professionals, more aware of encephalitis in terms of early diagnosis, treatment and rehabilitation process then the book has succeeded. It will be improved upon one day but certainly it will serve its purpose for a long time to come. Incidentally, I like the design and layout and as DVD's go, it is well produced.

Reviewed by: Dr Rudy Capildeo,
Brentwood Hospital,
Brentwood, Essex, UK.

Cognitive Neurology: A Clinical Textbook



Editors: Stefano F Cappa,
Jubin Abutalebi,
Jean-Francois Demonet,
Paul Fletcher and
Peter Garrard
Published by: Oxford University Press;
1 edition (28 Feb 2008)
Price: £49.95
ISBN: 9780198569275

Neurology in the UK sits within the group of physicianly specialties. Most UK neurologists, in order to get MRCP, will have been on medical rotations comprising cardiology, gastroenterology etc. While this can be helpful when managing a sick neurological in-patient with multi-system disease, it must be admitted that a knowledge of some medical subspecialties is of little value to the neurologist most of the time. Due to the quite separate training structures for neurology and psychiatry, most neurologists will not, however, have done any psychiatry, not even a six month SHO post. This is regrettable given that a knowledge of psychiatry is so helpful and indeed necessary to practise good neurology. It is particularly unfortunate, however, for those who practise in the borderland between neurology and psychiatry, namely cognitive neurology.

Due to the traditional lack of neurologists in Britain, many neurological diseases are managed by non-neurologists. As neurology has expanded, this has led to some jostling with other specialties for conditions such as stroke and Parkinson's. Most dementia is assessed and treated by old age psychiatry, who have multi-disciplinary teams well set up to manage the overall requirements of dementia patients and their families. This raises the question of what role, if any, does neurology have in the dementias. Traditionally, it is younger patients and those with atypical presentations who are seen in neurology. This is mainly due to neurology having better access to investigation in order to refine the diagnosis, but services for the ongoing management of dementia patients tend to be in old age psychiatry settings.

Focal cognitive deficits, whether due to stroke or tumour, or cognitive deficits due to disease, such as multiple sclerosis or epilepsy, are managed by the relevant neurological subspecialist.

Memory and cognitive disorders clinics have sprung up in a few of the larger neurology centres, and are mainly concerned with investigating memory complaints, the bread and butter being differentiating early dementia, mild cognitive impairment and psychological causes of impaired memory. A few of the more esoteric focal cognitive disturbances also present in such clinics.

This multi-author text has been written to provide an introduction to the field. After an introductory section on investigation (neuropsychology, imaging and neurophysiology), there is a useful section with chapters on the various focal deficits. In additional to covering the usual suspects (memory, language, etc.) there is a helpful chapter on neurobehavioural disorders after stroke.

The dementias section has a helpful chapter on differential diagnosis, followed by descriptions of the four commonest causes of dementia. These chapters achieve a useful balance between the clinical features and underlying pathology.

There then follows a section covering areas sometimes neglected in other cognitive texts, namely trauma, MS, epilepsy, schizophrenia and depression. Lastly, to illustrate that diagnosing cognitive disturbances is not an academic exercise, there follows a useful section on drug treatment and rehabilitation of cognitive disorders.

The book is excellently referenced. While bigger tomes covering this area exist (e.g. Rizzo & Eslinger), this book nevertheless provides a very useful introduction to cognitive neurology. It will be of use to neurologists, psychiatrists, psychologists and others interested in this field.

Reviewed by: John Greene, Institute of Neurological Sciences,
Southern General Hospital, Glasgow, UK.

Greenfield's Neuropathology 8th Edition

Authors: Seth Love, David N Louis, David W Ellison
Published by: Hodder Arnold
Price: £475.00 + VAT
ISBN13: 9780340906828

Greenfield's needs no introduction within the field of neuropathology. It is the primary reference text referred to by training and practising neuropathologists alike. This edition co-incidentally marks the 50th anniversary of the first edition of the book. The editors, from both sides of the Atlantic, have drawn upon the expertise of over seventy contributors from across the globe. More than half of these contributors are new. The result is a dramatic refinement and re-working of the previous edition, which itself stood out as a remarkable text.

The stated aims of this book are "to provide an authoritative, comprehensive account of the pathological findings in neurological disease, their biological basis and clinical manifestations…underpinned by a clear description of molecular and cellular processes…". The editors have clearly achieved these aims with flourish. Much of the historical data has been removed, and replaced by recent research data, providing a modern and up-to-date stance. A reference text is usually used to provide an answer to a specific question, or to help the reader understand a single disease entity. This book is distinct in its digestability. It is possible to read a chapter in one sitting and retain much of it, and that is a real achievement in writing.

This new edition contains more illustrations and tables, many of the former are new and all are good quality. The images are also available on the dvd, and, usefully, the publishers state that they can be used for non web-based teaching as long as the copyright label is visible. This makes the dvd incredibly useful for personal use, and also a fantastic resource for lectures.

This new edition has a different focus. The introductory chapters from previous editions have been sacrificed for more detail elsewhere. The ophthalmic chapter has also been withdrawn. These changes are an understandable evolution. While the value of the lost chapters is undeniable, they are well represented in other books. The result is a collection of approachable chapters that stand alone as complete authorities and are arranged in a logical order.

This edition has an altered layout. The book still feels pleasant to handle, and has maintained its "quality feel". Page numbering is now continuous between the two volumes, preventing the frustration of picking up the wrong volume that I personally suffered with in the last edition. The new edition is a similar length to its predecessor. The index, however, is shorter and only present at the back of volume II. This, and the lack of the page-keeper ribbons are two oversights that are minor compared to the book's many strengths.

This new-and-improved Greenfield's has exceeded my expectations and is likely to take up a much-used place on many Neuropathologists' bookshelves. It is also invaluable to other clinicians within the field, enhanced by the closer links with clinical data that this edition enjoys. I imagine the shift in emphasis towards genetic and research data, often from animal models of disease, will increase the readership of this book to include more from the non-clinical research community. There is simply nothing in paper-form that compares with it.

Reviewed by: Nicki Cohen, SpR Neuropathology, Southampton, UK.

Future directions of the Association of British Neurologists

As Neurologists, we face many pressures and changes in our working practices. Guidelines, recommendations, reports, new models of inpatient and outpatient care, re-appraisal and revalidation, inundate us. At the same time, the daily work remains. This is the heart of what we do and love: in our clinics, in the laboratory, and on the wards. It is easy to feel swamped by external guidelines and protocols.

Reflecting our daily lives, the Association of British Neurologists (ABN) must also juggle many activities to pro-actively influence the direction of our work. If we are passive, we have no voice in shaping our future, or the future care of our patients.

The ABN must provide and facilitate education, communication, research, and guidelines for Neurologists, both in their clinical and scientific work.

Education is central to the function of the ABN. Its focus is to organise stimulating and inspiring meetings. These gatherings bring together basic science, clinical practice and new developments with national and international speakers, scientific presentations, teaching sessions, along with platform presentations and posters from members at all stages of their careers. The structured components of meetings need to be complemented by informal discussions amongst academic and clinical neurologists at both consultant and training stages of their careers.

Figure: The Association's Coat of Arms, unveiled in April 2007, is a symbol of the aims and achievements of the ABN.

To further this aim, and with support of most members, the ABN is planning an exciting new development. From 2009, we will hold a single five-day meeting instead of the former bi-annual three-day meetings. We are providing a forum for greater depth of teaching and scientific sessions, along with more time for informal discussions and exchange of ideas.

The first of these new-look meetings will be in Liverpool from 22-26 June, 2009, at the Arena and Convention Centre. This Joint meeting with the Spanish Neurological Society includes scientific sessions on stroke, infectious diseases and dementia, along with teaching sessions on important clinical topics ranging from neuropathy to epilepsy.

The ABN will also continue to facilitate education through regular news in *ACNR*, and distribution of the JNNP quarterly supplement 'Neurology in Practice' and Practical Neurology to members. The Association supports neurologists with travel expenses for research projects and educational visits to economically less-developed countries. As a result, the ABN Africa Neurology Interest Group has produced a CD entitled 'Neurology Teaching Resource for African students'.

At this turbulent time, future consultants continue to have an active representation on Council, and the Association provides administrative support to ABN Trainees. The need for ABN input into sound training programmes cannot be overestimated: this is our future. The Training and Education Committee (TEC) advises the Association on matters relating to undergraduate education, postgraduate training, continuing professional development and relevant issues in Europe. The Association is pro-active in Knowledge-based assessment, and provision of student bursaries and annual prizes.

2008 sees a face-lift for the ABN website. It will be more attractive, and easier to use. New features will include an improved online forum for members and useful information for the general public and other medical societies. The monthly electronic newsletter updates members on developments.

The Association administers and funds the British Neurological Surveillance Unit, assisting researchers investigating rare neurological conditions on a national scale. The electronic system has been upgraded in 2008, greatly enhancing its use. The Clinical Research and Academic Committee (CRAC) will now link this to their work, building on this potential for research in a number of other neurological conditions. The ABN is part of the Joint Neurosciences Council. It plays an active and important role in practice guidelines, working with the Royal College of Physicians and NICE to do so, and with the Department of Health, for example in the implementation of the National Service Framework for Long Term Conditions.

The Services and Standards Committee looks at standards of neurological care, organisation and distribution of neurological services in the United Kingdom, including manpower monitoring, standards development and advice regarding commissioning. We have great opportunities for taking a lead in acute neurological care, such as stroke. The Committee's function is also vital in protection of consultant time for professional development and research.

The ABN is an important facility for us, and a unified focus. Things are changing and we have a choice between shaping our future and our patient care, or having its shape imposed on us. Your participation is vital. The ABN is taking a pro-active role in a new format for revitalised annual meetings, an improved website and enhancement of research potential. These changes are essential to stimulating excitement about being a neurologist, in keeping abreast with the enormous changes in both the science and practice of neurology and in facilitating communication between members and our community.

Heather Angus-Leppan MSc (Ep) MD FRACP FRCP was born in South Africa, trained in Australia and won a Scholarship as Visiting Australasian Registrar to the Radcliffe Infirmary, Oxford, in 1993. She is Head of the Neurology Department at Barnet Hospital and Consultant Neurologist, Honorary Senior Lecturer and Epilepsy Lead at the Royal Free Hospital, London, UK. She is the Honorary Assistant Secretary of the Association of British Neurologists, Honorary Secretary of the Neurosciences Section of the Royal Society of Medicine and current Chair of the Map of Medicine Epilepsy Group, UK.

Correspondence to:
Heather Angus-Leppan,
Honorary Assistant Secretary,
ABN.
Email. Heather.Angus-Leppan@bcf.nhs.uk

Nineteenth Meeting of the
European Neurological Society

June 20–24, 2009

Milan, Italy

Neurology: Learning, knowledge, progress and the future

Key symposia:

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

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

Abstract Submission Deadline: February 11, 2009
Early Registration Deadline: April 22, 2009

For further information please contact:
ENS 2009, c/o AKM Congress Service
Association House, P.O. Box, CH-4002 Basel / Switzerland
Phone +41 61 686 77 77 Fax +41 61 686 77 88 Email info@akm.ch

www.ensinfo.org

To list your event in this diary, email brief details to Rachael Hansford at rachael@acnr.co.uk by 8 December, 2008

2008

November

International Symposium on ALS/MND
3-5 November, 2008; Birmingham, UK
E. pam.aston@mndassociation.org

P-CNS meeting
6 November, 2008; Cardiff, UK
www.p-cns.org.uk

One headache after another
6 November, 2008; Royal Society of Medicine, London, UK
E. cns@rsm.ac.uk
www.rsm.ac.uk/cns

Adverse Psychiatric Side Effects of Medicines: What's Your Responsibility?
6 November, 2008; London, UK
T. 01243 775561
E. april@eyas.co.uk

Clinical Conundrums in Epilepsy, Epilepsy Syndrome Series meeting
7 November, 2008; RCP London, UK
E. olga.howard@ucb-group.com
T. 07979 532104

A New Sense of Self: Coping with the social and behavioural changes following ABI in childhood and adolescence
10 November, 2008; Nottingham, UK
www.trust-ed.org/news.html

Posture & Balance in Neurological Conditions, upper limb, Assistants level staff
10 November, 2008, Derby, UK
T. 01332 254679
www.ncore.org.uk

European Charcot Foundation University Classes in Multiple Sclerosis V
12 November, 2008; Taormina (Sicily) Italy
www.charcot-ms.eu

Epilepsy and Co-morbidities Conference
14 November, 2008; London, UK
E. jacob.k.burd@pfizer.com
T. 07968 439 662

Best Practice Meeting: molecular diagnostics of Duchenne and Becker muscular dystrophies
14-16 November, 2008, Amsterdam, Netherlands
www.emqn.org/emqn/

4th Essential Neuro MRI Study Day- One day course in interpretation of MRI Brain & Spine
15 November, 2008; Liverpool, UK
Kath Tyler, T. 01515295416/5552
E. essentialneuromri@hotmail.co.uk

Posture & Balance in Neurological Conditions, upper limb, Qualified staff
15-16 December 2008; Derby, UK
NCORE – T. 01332 254679
www.ncore.org.uk

Normal Movement for Musculoskeletal Therapists
15-16 November, 2008; Doncaster, UK
E. info@physiouk.co.uk

Neuroscience 2008 – Society for Neuroscience
15 -19 November, 2008, Washington, USA
T. 001 202 962 4000

International Symposium on Rare Diseases Inherited Neuromuscular Diseases: Translation from Pathomechanisms to Therapies
16-18 November, 2008; Valencia, Spain
http://tinyurl.com/valencia-symposium

Neonatal Cerebral Investigation
17-18 November, 2008; London, UK
T. 020 7594 2150
E. sympreg@imperial.ac.uk

West of England Seminars in Advanced Neurology
20-21 November, 2008; Exeter, UK
E. cgardnerthorpe@doctors.org.uk

Advanced Cognitive Rehabilitation Workshop
21-22 November, 2008; London, UK
E. enquiries@braintreetraining.co.uk
www.braintreetraining.co.uk

Benign Paroxysmal Positional Vertigo
22 November, 2008; Reading, UK
E: info@physiouk.co.uk

3rd National Conference: Autism Today
26-27 November, Manchester, UK
T. 0207 501 6711
E. amy.t@markallengroup.com

UKABIF Conference & AGM 'Whither The NSF For Long-Term Conditions'
27 November, 2009; London, UK
Chloe Hayward, T. 01752 601318
E. ukabif@btconnect.com

December

RAatE 2008
1 December, 2008; Coventry, UK
www.raate.org.uk

Nanoscale imaging and force measurements in Life Sciences
2 December, 2008; Oxford, UK
T. 01223 815645
E. drew.murray@jpk.com

3rd UK Stroke Forum Conference
2-4 December, 2008; Harrogate, UK
E. ukstrokeforum@stroke.org.uk
www.ukstrokeforum.org

6th National Bipolar Disorder Conference
5 December, 2008; London, UK
T. 0207 5016 711
E. amy.t@markallengroup.com

BISWG -Brain Injury - Focus on Practice
5 December, 2008; Edinburgh,UK
E. fenparry@jspsc.co.uk or
mhairi.mckay@lpct.scot.nhs.uk
www.biswg.co.uk

Brain and Behavior
5-6 December, 2008; New Orleans, USA
T. 001 504 988 5466
E. cme@tulane.edu

62nd Annual Meeting of the American Epilepsy Society
5-9 December, 2008; Seattle, United States
E. csluboski@aesnet.org,
T. 001 860 586 7505

Balance Study Day
6 December, 2008; London, UK
E. info@physiouk.co.uk

Balance Treatment Workshop
7 December, 2008; London, UK
E. info@physiouk.co.uk

Brainstem: neural networks vital for life
8-9 December, 2008; London, UK
T. 020 7451 2500
E. discussion.meetings@royalsociety.org

Human Brain Tissue Research
11-12 December, 2008; Munich, Germany
E. conference@brainnet-europe.org
www.brainnet-europe.org/conference

39th Heart and Stroke Clinical Update
11-13 December, 2008; Toronto, Canada
T. 416 489 7111
E. prof.ed@hsf.on.ca

Stroke in the Real World - XVII SINV Meeting
11-13 December, 2008; Montecatini Terme, Italy
T. 39 0 572 913 388
E. silviapolvani@vittoriacongressi.com

The British Neuropsychiatry Association – Teaching Weekend
12-14 December, 2008; Oxford, UK
E. admin@bnpa.org.uk
jashmenall@yahoo.com
www.bnpa.org.uk

2009

January

Normal Movement for Musculoskeletal Therapists
10-11 January, 2009; Marlborough, UK
E. info@physiouk.co.uk

4th Congress of the International Society for Vascular Behaviourial and Cognitive Disorders
14-16 January, 2009; Suntec, Singapore
www.vas-cog.org/vas-cog2009,
T. +46 31 708 60 00
E. vas-cog2009@congrex.com

Neurological Upper Limb for OTs
15 January, 2009; Derby, UK
NCORE
T. 01332 254679
www.ncore.org.uk

Epilepsy Study Day
20 January, 2009; Derby, UK
NCORE
T. 01332 254679
www.ncore.org.uk

Biomarkers in Brain Disease Conference
26-28 January, 2009; Oxford, UK
Dr Stacie Bloom, T. 001 212 298 8610
E. SBloom@nyas.org

Institute of Psychiatry's 6th National Conference of Research in Medium Secure Units
29 January, 2009; London, UK
www.iop.kcl.ac.uk/events

Normal Movement for Musculoskeletal Therapists
31 January-1 February, 2009; London, UK
E. info@physiouk.co.uk

February

2009 Drug Discovery for Neurodegeneration, presented by the Alzheimer's Drug Discovery Foundation
2-3 February, 2009; Washington, USA
T. 001 773 784 8134
E. meetings@worldeventsforum.com

The Society for Research in Rehabilitation Winter 2009 Meeting
3 February, 2009; Derby, UK
E. patricia.dziunka@srr.org

The British Neuropsychiatry Association Annual General Meeting
5-6 February, 2009; London,UK
E. admin@bnpa.org.uk jashmenall@yahoo.com
www.bnpa.org.uk

The President's Prize, Clinical presentations
5 February, 2009; Royal Society of Medicine, London, UK
E. cns@rsm.ac.uk www.rsm.ac.uk/cns

Kinetic Control: Movement dysfunction for the neurological patient (Part b)
5-7 February, 2009; Derby, UK
NCORE
T. 01332 254679
www.ncore.org.uk

37th Annual INS Meeting
11-14 February, 2009; Atlanta, Georgia, USA
International Neuropsychological Society
T. + (614) 263-4200
F. + (614) 263-4366
E. ins@osu.edu

Vagal Nerve Stimulation: from both sides of the border
13th February, 2009; Glasgow, UK
Nicole Wright, Epilepsy Scotland,
T. 0141 419 1709

Splinting for the Neurologically Impaired Hand
24 February, 2009; Derby,UK
NCORE
T. 01332 254679
www.ncore.org.uk

11th National Dementias Conference
26-27 February, 2009; London, UK
E. annehaylock@markallengroup.com

RCN Rehabilitation and Intermediate Care Nursing Forum Conference
27-28 February, 2009; London, UK
E. Mirka.Ferdosian@rcn.org.uk
T. 020 7647 3583

Trans-cultural rehabilitation: an inter-professional conference exploring culture and diversity in rehabilitation
27-28 February, 2009; London, UK
E. rehabilitation@rcn.org.uk
www.rcn.org.uk/events

March

After meningitis – Living with the impact of meningitis and meningococcal septicaemia
4 March, 2009; London, UK.
E. janeb@meningitis-trust.org
www.meningitis-trust.org

1st UAE International Meeting on Diagnosis and Treatment of the Neurogenic Bladder in Children and Adolescents
7-8 March, 2009; Abu Dhabi, UAE
E. mpatricolo@skmc.gov.ae

Restauracion Neurologica – 3rd International Conference
9-13 March, 2009; Havana, Cuba
E. rn2009@neuro.ciren.cu,
Professor Jorge Bergado,
Jorge.bergado@infomed.sld.cu
www.ciren.cu

9th International Conference on Alzheimer`s and Parkinson`s Diseases - ADPD 2009
11-15 March, 2009; Prague, Czech Republic
T. Natalie Shabi, 41 229 080 488
E. adpd@kenes.com

5th World Congress World Institute of Pain
13-16 March, 2009; New York, USA
Natalie Shabi, Tel. 41 229 080 488
E. wip@kenes.com

4th Fred J. Epstein International Symposium on New Horizons in Pediatric Neurology, Neurosurgery and Neurofibromatosis
15-19 March, 2009; Eilat, Israel
Hannah Baum T. 972 3 517 5150
E. newhorizons@targetconf.com

3rd Meeting of the Parkinson's Disease Non-Motor Group
21 March, 2009; London, UK
E. yogini.naidu@uhl.nhs.uk

Marseille Neurosurgery 2009 Joint Annual Meeting of the European Association of Neurosurgical Societies (EANS) and the French Neurosurgical Society (SFNC)
27-31 March, 2009, Marseilles, France
www.kenes.com/eans-sfnc

9th London International Eating Disorders Conference
31 March – 2 April, 2009; London, UK
Amy Tranter, T. 0207 5016 711
E. amy.t@markallengroup.com

Brain Repair Spring School 2009
31 March – 2 April, 2009; Cambridge, UK
T. 01223 331160
E. pj214@cam.ac.uk

11th International Neuroscience Winter Conference
31 March – 4 April, 2009; Solden, Austria
Professor Tsolakis, T. 43 51 250 423 715
E. philipp.tsolakis@i-med.ac.at

April

20th National Meeting of the British Neuroscience Association
19-22 April, 2009; Liverpool, UK
Dr Yvonne Allen, E. bna2009@liv.ac.uk

Wiring the Brain
21-24 April, 2009; Adare, Ireland
E. wiringthebrain@gmail.com
www.wiringthebrain.com

61st Annual Meeting of the American Academy of Neurology
25 April- 2 May, 2009; Seattle, WA, USA
www.aan.com

May

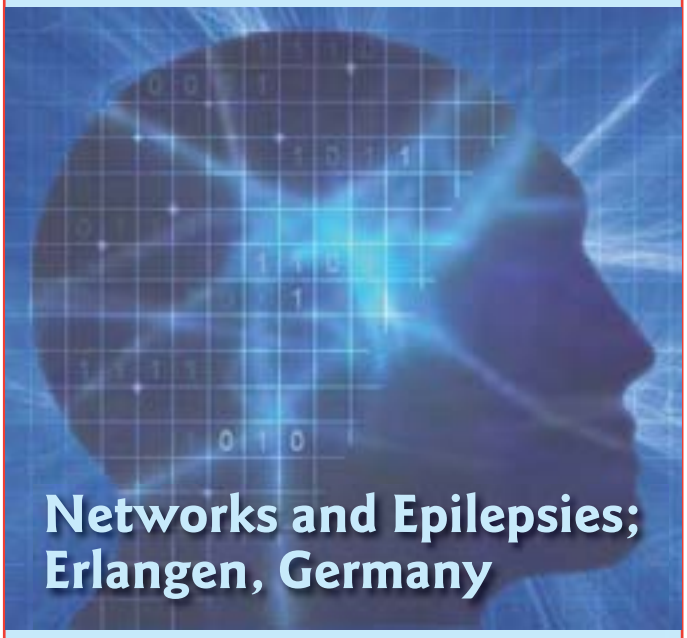
Neuropsychiatric, Psychological and Social Developments in a Globalised World
5-8 May, 2009; Athens, Greece
Mrs Demy Kotta, T. 302-106-842-663
E. appachellas@yahoo.gr

Molecular Mechanisms Of Neurodegeneration
8-10 May, 2009; Milan, Italy
Angelo Poletti, T. +390250318215
E. triplets@unimi.it

5th ISPRM World Congress
9-13 May, 2009; Istanbul, Turkey
E: traceymole@wfnr.co.uk

5th Epilepsy Colloquium Erlangen

19-20 June, 2009



Email: claudia.saint-lot@uk-erlangen.de
www.epilepsiezentrum-erlangen.de

Centre for Community Neurological Studies

Continuing Professional Development (CPD) (All completed by distance-learning)

leeds metropolitan university

Masters courses:
- Epilepsy Practice
- Multiple Sclerosis Practice

(Postgraduate certificate, Postgraduate Diploma, full MSc)

Single module course:
- Multiple Sclerosis Care in the Community

(15 credits at Level 3)

Professional diploma courses:
- Epilepsy Care
- Multiple Sclerosis Care
- Parkinson's Disease Care
- Stroke Care

(All 45 credits at Level 3)

The Centre has been delivering distance learning courses for more than a decade and over 1000 health professionals from all parts of the UK have already obtained CPD qualifications from us. Our courses are becoming essential qualifications for those who want to specialise in or lead neurological services.
The key aim of all our courses is to apply the knowledge gained into professional practice. The main outcome should be enhanced clinical practice.

Contact Details
For more detailed information on our courses please contact:
The Centre Administrator, Tel: 0113 812 5918, Fax: 0113 812 3416
Email: ccnsenquiries@leedsmet.ac.uk

Courses developed in association with: NeuroEducation, Epilepsy Action, Multiple Sclerosis Society, Multiple Sclerosis Trust, Parkinson's Disease Society

BNPA

THE BRITISH NEUROPSYCHIATRY ASSOCIATION

Annual Meeting

February 2009

The BNPA is pleased to announce their
22nd Annual General Meeting
5/6 February 2009
With a joint meeting (4 February)
for the Section of Neuropsychiatry,
Royal College of Psychiatrists

Venue
The Institute of Child Health, Guilford St, London

- All you need to know about the limbic system
- Psychopharmacology in neuropsychiatric settings
- Tourette's and OCD,
- Mechansims of Psychosis
- Neuroscience and Society

A more detailed programme and booking form can be found on our website **www.bnpa.org.uk**
For details of exhibition/sponsorship opportunities, contact:
Jackie Ashmenall on
Phone/Fax 020 8878 0573 / Phone: 0560 1141307
Email: admin@bnpa.org.uk or jashmenall@yahoo.com

British Neuropathological Society

110th Meeting of the British Neuropathological Society

January 7-9th 2009
Venue: Institute of Child Health, Guilford Street, London WC1N 1EH

Symposium: "New perspectives in Parkinson's Disease".
Organiser: Professor Tamas Revesz, UCL Institute of Neurology, London, UK
Speakers: Professor Andrew Lees, London, UK
Professor David Brooks, London, UK
Professor Maria Spillantini, Cambridge, UK
Professor Nicholas Wood, London, UK
Professor Patrik Brundin, Lund, Sweden
Alfred Meyer Lecture Memorial Lecture:
Professor Dennis Dickson, Jacksonville, Florida

- Full programme of talks and posters
- The Society Dinner to be held at The Honourable Society of Gray's Inn

We welcome Neuropathologists, Neurologists and Neuroscientists to a meeting attracting a wide range of speakers from the UK and abroad. Trainees in Neuropathology and Neurology are particularly encouraged to attend. Join us for a full academic programme with an excellent opportunity to meet and discuss professional and academic matters.

Full details: http://www.bns.org.uk/

British Association for Cognitive Neuroscience (BACN) Conference

1-3 September, 2008; Swansea, UK.

View of Swansea Bay and the University Campus.

The annual conference of the British Association for Cognitive Neuroscience (BACN) was held from September 1st - 3rd at the University of Swansea (picture). The association is home to UK cognitive neuroscientists from a variety of backgrounds, ranging from psychophysiologists (BACN emerged from the British Psychophysiology Society) to those with a background in neuroimaging. The Association prides itself on the friendly and supportive atmosphere of its annual meetings and is particularly welcoming to scientists at the start of their career. International visitors this year travelled as far as from Taiwan and Kenya.

The first symposium was devoted to the auditory basis of language learning impairments, especially those associated with specific reading disability (SRD) and specific language impairment (SLI). Dr Halliday (UCL, Oxford) showed impaired auditory processing in SRD but preserved ERP evidence for auditory cortical maturation. Dr Baker (UCL) reported that ERP indices of delayed auditory processing in SLI were correlated with reduced basal ganglia grey matter density. Dr Hamalainen (Cambridge) reviewed behavioural and ERP studies of sound processing in SRD and concluded that deficits in sound onset perception were the most consistent deficit. A keynote from Prof Scott (UCL) reviewed recent progress in mapping brain networks for speech comprehension and their link to speech production. Of interest was the sensitivity of the left anterior temporal cortex to speech intelligibility and the involvement of a posterior superior temporal region to sensorimotor integration, which supports the notion of a dual stream model of speech perception.

They reported altered brain function (EEG) and slower speed of cognition but normal neurological functions in those children living above 3500m

The second symposium was dedicated to recent advances in cognitive neurophysiology (ERP and EEG). Representatives from major ERP system manufacturers demonstrated their newest developments, ranging from automated artefact correction methods (Gutberlet, Brain Products), low resolution electromagnetic tomography (van de Velde, ANT) to multimodal image registration and volume conductor models for EEG source localisation (Fuchs, Compumedics Neuroscan). The developers of Statistical Parametric Mapping (SPM) gave an introduction to Dynamic Causal Modelling (DCM), a novel SPM extension for hypothesis-driven exploration of electrophysiological and neuroimaging data (Kilner, UCL). The plenary talk by Prof Stam (Amsterdam) was dedicated to the emerging application of modern network theory to disruption of functional brain networks in human brain diseases such as Alzheimer's disease, schizophrenia and epilepsy.

Among the numerous high quality open-platform presentations, the study by Dr Hogan and colleagues (Southampton, UCL, Universities of Granada and Western Australia, Univalle and UPSA Bolivia) deserves a mention. They used modern cognitive neuroscience methods (psychometrics, ERP and EEG) in a large-scale field study in Bolivia to evaluate the adaptation of cognition to high-altitude living in infants and children. They reported altered brain function (EEG) and slower speed of cognition but normal neurological functions in those children living above 3500m.

This year's BACN conference was jointly organised with the Welsh Institute for Cognitive Neuroscience, which held its inaugural meeting in Swansea. Its symposia included advances in the cognitive neuroscience of memory. The plenary lecture was given by Dr Wilding (Cardiff) on ERP studies of memory retrieval. Of particular interest was also the report by Vann and colleagues (Cardiff, Bristol, Manchester) on a large cohort of patients with colloid cysts and variable degree of fornix and mamillary body damage which resulted in selective loss of memory recall with preservation of recognition abilities.

Torsten Baldeweg,
UCL Institute of Child Health,
University College London (UCL), UK.

The next Annual meeting will be held from 21st-23rd September 2009 in London, at the UCL Institute of Child Health. Symposia will cover topics such as neural plasticity in cognition and advances in multimodal neuroimaging.
Those interested in hosting a symposium at this meeting should contact T.Baldeweg@ich.ucl.ac.uk

ABN Autumn Scientific Meeting
A fond farewell to biannual ABN meetings

10-12 September, 2008; Aviemore, UK.

Falling asleep on the outskirts of London and waking in the Scottish highlands on board the Caledonian Sleeper was a perfect start to the last 'old-style' ABN conference, held in the beautiful setting of Aviemore.

A stroke symposium reflected the current political importance of this area, and the increasing engagement of neurologists in stroke medicine. Dr Malcolm Macleod discussed the reasons for the failure of translation from successful treatments in animal models of stroke into clinical benefits in patients. He dramatically illustrated the impact of low power, lack of randomisation and blinding and failure to model co-morbidity in animal models. These problems, equally significant in animal models of neurodegeneration, suggest the need for radical changes in the approach to pre-clinical therapeutic studies. Dr Ed Littleton presented the results of an audit of the introduction of a 24 hour thrombolysis service. The audit found that paramedics and A&E triage nurses find it difficult to use the 'FAST' assessment system appropriately, and suggests that models of thrombolysis delivery need to be carefully designed to avoid negative impacts on neurology training.

The short scientific papers given by members were of consistently high quality. Dr J Jones presented three-year follow-up data from the trial of alteluzumab (Campath) in early active multiple sclerosis. A clear reduction in progression of disability in the treated group may herald an important breakthrough in MS treatment from the ongoing Phase III trials. Dr Sarosh Irani described the clinical features and natural history of sub-acute encephalopathy associated with NMDA receptor antibodies in a cohort of 31 patients. This syndrome appears to have a very distinctive phenotype. Presentation with psychiatric symptoms is followed by seizures, reduced conscious level, autonomic instability and movement disorder. Further studies of antibody levels in disease control groups will establish the specificity of the diagnostic assay.

The ABN medal was presented to Dr John Morgan-Hughes. He provided an inspiring overview of his scientific legacy, which is particularly remarkable for having been achieved whilst working as an NHS clinician in a small research group.

A highland banquet and celidh, as well as a mini-triathlon, allowed delegates to make the most of their time in Scotland. Despite looking forward to the new format of a five day annual conference, many will look back fondly on our last small and traditional ABN meeting.

Biba Stanton, ABN Trainees Committee Secretary, Royal Free Hampstead NHS Trust.

delegates at the ABN

The Association of British Neurologists' 2008 autumn meeting in Aviemore was followed by a unique sporting event. Some 23 members of the Association took part in the first ever 'ABN mini-triathlon', which benefitted from glorious sunshine, spectacular scenery and the stunning backdrop of the Cairngorm Mountains.

Competing over a 'modified super-sprint' distance, the entrants swam sixteen lengths of the hotel pool, before exiting the hotel past startled onlookers, to pick up their pre-hired mountain bikes from the car park. They then cycled over a 6.5 km course which included a fairly punishing uphill component, a short rocky technical section – which clearly favoured experienced mountain bikers - and a fast forest track back to the hotel for the cycle-run transition. A final 2.5km run through the woods of the Rothiemurchus estate returned the competitors to the finish line at the Hilton Coylumbridge.

The event was won by Dr Richard Davey, consultant neurologist in Wakefield with a time of 30 minutes 30 seconds. Dr Ursula Schultz from Oxford was a close second, arriving at the finish line some 58 seconds later. Entrants included a past President of the ABN, Professor Charles Warlow, who completed the entire course in a commendable 61 minutes. All the finishers were awarded a medal and a commemorative T-shirt.

Finishers of the Triathlon.

European Federation of Neurological Societies (12th Congress)

23-26 August, 2008; Madrid, Spain.

With the profusion of neurological congresses around the world, many dedicated to specialist and subspecialist interests, it is perhaps inevitable that a general neurological congress will not be the forum at which investigators will wish to announce startling new findings. It may be said that the emphasis is more on encouraging us, the foot soldiers of neurology, to retain the information which is already in the public domain, with any gain of new information being a bonus. Hence, the arena of focused workshops and satellite symposia, amongst which the following proved helpful to my waning cognitive powers of factual retention. The limitations of functional imaging in the trigemino-autonomic cephalalgias, showing activation of the neural pain matrix, were emphasized, prior to a 'stimulating' account of the possible place for neurostimulation in these conditions. One literature review has suggested >60% efficacy in chronic drug-resistant patients, but the drawbacks are many: weeks to months before improvement occurs, the risk of adverse effects from surgery, the generator or the electrodes, and the current absence of any double-blind studies (1 apparently ongoing in France). The latter will require homogeneous patient selection criteria, agreed assessment methods and long-term follow-up.

A lecture on advances in genetics in movement disorders demonstrated how these findings have increased understanding of disease pathogenesis, for example in Parkinson's disease, specifically in terms of mitochondrial dysfunction and misfolded protein toxicity. Parkin, PINK1, and DJ1 all encode proteins which normally protect neurones from oxidative stress and regulate mitochondrial morphology, whilst α-synuclein and LRRK2 proteins become misfolded and aggregate. The possible importance of autophagy, a constitutive lysosomal mechanism to protect neurones, was introduced: knockout of this process in animal models leads to neurodegeneration, which may be relevant in the rare Kufor-Rakeb disease.

Some conditions which are only occasionally seen in the general neurology clinic, and hence in congress symposia, made welcome appearances. A focused workshop on myotonic dystrophy covered the genetics of DM1, wherein the correlation between increased trinucleotide repeat size in the DMPK gene and disease severity does not necessarily permit accurate prognosis, with some families showing a variable phenotype despite the same number of repeats. Missed diagnosis of both DM1 and DM2 seems common because the presentation is often to other, non-neurological, specialties, in DM1 including ophthalmology, cardiology, O&G, and paediatrics, although neurologists are not immune from error, the differential diagnosis of DM2 encompassing inflammatory myopathies, mitochondrial myopathies, acid-maltase deficiency, FSH dystrophy, fibromyalgia and iatrogenic myopathy. In view of the systemic nature of DM1, a plea was made to rename the disorder as 'Batten-Gibb syndrome' since these individuals described the systemic features in 1909, the same year that Steinert emphasised the muscular problem which has formed the basis for disease nomenclature ever since.

Treatment of Friedreich's ataxia, hitherto entirely symptomatic, was the focus of a drug-company sponsored symposium. Idebenone may have effects on the cardiomyopathy and possibly also the neurological features. The increased understanding of disease pathogenesis, stemming from the identification of the underlying genetic mutations and the functional roles of frataxin, has prompted the possibility of disease-modifying treatment, for example with iron chelation.

As a medical student in the last century, I got interested in the possible viral pathogenesis of multiple sclerosis. The subject still lives, with a symposium on herpes viruses looking at their potential causative roles in MS (EBV, HHV6, VZV), Behçet's disease (HSV1), and Bell's palsy (HSV1). Furthermore, it has been noted that similar brain areas are injured in herpes simplex encephalitis and Alzheimer's disease, with anecdotal reports of HSV1 infection in dementia brains, and in vitro and in vivo evidence of increased Aβ production associated with HSV1. CSF PCR remains the gold standard for diagnosis of herpes simplex encephalitis, although may be negative if testing is very early or late in the disease course. The role of steroids remains uncertain, no randomised study having yet been performed, although a retrospective study (JNNP 2005;76:1544-9) found poor outcome in patients who did not receive steroids.

Amongst the more than 1500 scheduled poster presentations, I noted two describing parkinsonism of late onset in type 1 Gaucher's disease: this may apparently look identical to idiopathic Parkinson's disease. In a French national prospective study, nearly a quarter of the patients developed parkinsonism. For those seeking advances in the treatment of neurological disease, three posters looked at the use of prolonged-release ropinirole (PREPARED study) which seems to produce better symptom control and levodopa sparing in advanced PD than standard ropinirole (I have already had enquiries from a patient).

A careful study (double-blind, placebo-controlled, crossover) from Newcastle suggested a possible role for levetiracetam in the treatment of MS intention tremor, but I was less convinced by a report from elsewhere of transcranial magnetic stimulation for MS ataxia. A trial from Iran of rivastigmine for memory disorder in MS found equal improvement in both treatment and placebo-control arms of the study, perhaps inevitable in a brief (12-week) study; the severity of the pre-treatment impairments in the MS patients did not appear to be mentioned. In a case study from Greece, rituximab was reported to be useful in neuromyelitis optica, in agreement with a larger study from the Mayo Clinic now being published (Arch Neurol).

For those for whom all this activity was too much, and a brief snooze required at the back of one of the lectures rooms, solace was at hand in the form of a poster documenting 'Inspiration from dreams in neuroscience research', relevant to two Nobel Prize Winners, Otto Loewi and John Eccles. As a Nature paper from 2004 stated, sleep inspires insight!

The History of Medicine session focused on the work of Santiago Ramon y Cajal, describing how his painstaking studies using the Golgi stain allowed him to develop the neurone theory, in succession to the reticular theory of Golgi, wherein the neurone was viewed as an autonomous unit in contact but not in continuity with other neurones, an infinitely fragmented system. The history tour visited the old Hospital de San Carlos, where there are several atmospheric lecture theatres including the Aula Ramon y Cajal where he used to teach; there is also a garden dedicated to him and a statue, the latter somewhat solemn and linear. Another Spaniard, lesser known outside his own country, Pedro Lain Entralgo (1908-2001), formed the subject of Ivan Iniesta's lecture which reviewed many of the works of this medical historian, and to whom the final words of this review may be given: 'the history of medicine is memory at the service of hope'.

AJ Larner, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.

WCTRIMS

17-20 September, 2008, Montreal, Canada.

As the biggest demyelination show in the world rolled into Quebec this September, Montreal struggled a little with the infrastructure required to support the hoards but her charm just about won through in the end. Despite its size, the meeting itself was a surprisingly modest affair. There were no scientific fireworks declared here, but WCTRIMS offered a nice review of the progress that has been made on several fronts over the past 12 months.

The teaching courses were popular and successful. It's a reflection of how far things have come in the past year that the advances in our understanding of aetiology; both in determining relevant environmental exposures, and even more strikingly the genetic contributors to susceptibility, are now part of "teaching" sessions rather than being trumpeted from on high as "key breakthroughs". It is also to the great credit of the investigators involved that the important lessons learned during the long struggle to reach this point have led to a sober and realistic view of how far we still have to go, and our ability to take those next steps.

In descriptive pathology, Esther Breij received a frosty reception from the audience in response to her inability to replicate the heterogeneity of the Luccinetti lesional classification system. 'Different selection criteria' was the uneasy but diplomatic conclusion. Perhaps MS is yet one disease? The great pathogenic debate of our times remains as an uneasy stand-off between the primary inflammatorists and the primary degenerates. However the debate as presented here meekly conceded the premise that inflammation drives the disease and resolved to a question of whether it primarily targets glia versus simultaneously targeting glia and neurons. Regardless, the more fundamental inflammatorists declaring MS to be a self-limiting disease may have overstepped the mark and were met by a gloriously Gallic non plussed response from the gathered audience. Happily, this response was also given to the other lot when their case was put forward. The Quebec charm may have contributed, or perhaps a communal sense was evidenced that descriptive pathology may still have the upper hand in declaring lesions that the MRI doctors miss, and the final say in taxonomy, but is fundamentally limited by its cross sectional approach. The natural historians can help, as can the therapists, but there was little news from either to further illuminate. The therapists tell us that Copaxone has now mirrored the BENEFIT, CHAMPS and ETOMS Trial results in delaying time to second event; and that the quest for oral DMTs is nearing a position of having something to say for itself, but the repair doctors still have nothing meaningful to offer to patients. For them (and I am one), achieving a more fundamental understanding of how remyelination occurs (and why it fails) remains the issue – there were no breakthroughs to be found in Montreal but steady progress in the roles of OPC guidance molecules, axo-glial interactions that contribute to axonal injury, and the metabolic microenvironment determinants of injury response.

The natural historians were not completely silent, telling us that while prognostication for the individual patient remains challenging, being non-white and young predicts a more severe early disease course. Interestingly, it seems that disease course is relatively stereotyped in both site and severity during the initial attacks; perhaps reflecting undiscovered genetic disease course modifiers. The Ebers group presented their evidence that the HLA DRB1*01 allele may have a beneficial effect on disease course through examination of allelic discordance in sib-pairs. This (admittedly limited) progress was briefly encouraging, however the mighty MSBase team were subsequently to confirm our worst suspicions that early disease is indeed the hardest for which to prognosticate, and that EDSS in the mid-ranges remains a lottery for the long-term outcome even at advanced disease duration time points. At least they were able to console us with news that (as we intuitively always suspected) patients who remain relatively free of disability, or who are heavily disabled at advanced disease durations, tend to remain as they are.

But with statements such as the last, one cannot get away from the limitations of our assessment measures. Poor responsiveness to real change 'at the ends of the ruler' used to measure that change might account for predictability in a fundamentally unpredictable disease. So are we any better, or will we be any better in the future at measuring our patients' disease burden? Not really is the conclusion from the evidence presented here. There are no new clinical tricks, and our MRI surrogates still present problems. Maria Pia Sormani tackled the problem by using clever statistics to bridge the clinico-radiological chasm; establishing 'ecological correlation' between accumulation of new T2 lesions and annualised relapse rates in the published trials, but concluding that we haven't yet reached the stage where 'causal correlation' can be established at an individual patient level. This leaves us in an interesting position where measuring T2 lesion load isn't pointless, but neither is it yet validated as clinically meaningful! The speaker's frustration was clear about the difficulties in advancing this work due to the possessiveness of investigators and companies over outcome data. Our intellectual isolationism means that replicating these promising initial efforts for atrophy measures is presently beyond even what the redoubtable Dr Sormani and her team can face. As an imaging footnote, the MR modalities embarrassingly still labelled as 'new' (MRS, MTR etc.) continue to search for their role as useful and interpretable endpoints. We will see.

In the absence of anything exciting to report, the therapists offered a fascinating meta-perspective on why there is nothing exciting to report – it seems that all the relapses have gone! The annualised relapse rate in placebo arms of DMT trials has fallen from around 0.8 in the pivotal studies to current levels of around 0.3. As a result, it has become hard in these difficult times to prove that our wonderful new treatments work, further compounded by the fact that those pesky ethicists won't let us use placebo arms anymore. So what is an MS researcher to do? The development of new 'platform' based study designs (where lengthy trials are performed to test the addition of novel vs placebo treatments onto existing best practice) seemed too sensible to ever catch on. The audience quietly reflected on the prospects of big Pharma accepting this vision for a brave new

world; regrettably we may have to waste a lot more time and money before desperation permits that kind of mature approach in developing better treatments for our patients.

Shamefully, cognitive dysfunction and rehabilitation remain the cinderella subjects of MS research. The relevant session was scheduled on the Saturday morning when most of the delegates had succumbed to fragility following a very fine Gala dinner the previous evening, opting instead to take refuge amongst Montreal's soothing diversions. A pity; if there was hope of new clinical endpoints that might take us forward, they were likeliest to be found here. Furthermore, those delegates who did attend found the draw of the competing "late breaking news" session too hard to resist. The last chance for fireworks went something like the following: regular high dose oral steroid courses further reduce relapse rates if you're still having them whilst on conventional DMT but are they not well tolerated (quel surprise), rituximab reduces MRI disease in PPMS but only if you have MRI disease to begin with, dosing with 40mg of Glatirimer Acetate is no better than 20mg and probably less well tolerated, phase III studies with anti-sense DNA molecules to silence VLA-4 will probably happen over the next 5-10 years, and that HHV-6A can induce a disease similar to MS in Marmosets.

Nevertheless, perhaps the real benefit of such an international gathering of MS professionals is to take an international view. A review of the current variation in availability of existing therapies was sobering. If "postcode prescribing" is problematic at a local level, the issue is compounded at an international level. Unsurprisingly, the rest of the world do not, and cannot, do as you do. On a purely immediate basis we could achieve much for the world's MS patients by addressing the global availability of existing therapies. As we heard here, the emerging generics are often more problematic than they might initially appear – being neither cheaper nor necessarily of equivalent safety and efficacy as their branded counterparts. WCTRIMS remains the only forum through which issues such as this can be highlighted and ultimately tackled.

Peter Connick
September 2008, Montreal, Canada.

PREVIEW Dementias 2009

February, 2009; London, UK.

The 11th national conference for all those working with patients suffering from dementia will be taking place in London in February next year. The 2-day conference, organised in association with the British Journal of Hospital Medicine, will give delegates a review and update on current developments in the dementias; in the fields of research, investigations, clinical care and service and policy issues.

The conference is aimed at all professionals involved with dementia, including old age psychiatrists, neurologists, geriatricians and physicians with an interest in the elderly; mental health service workers and team members, community nurses, hospital nurses and practice nurses.

Programme advisors Professor Tom Arie, CBE, Professor Emeritus of Health Care of the Elderly, University of Nottingham and Professor Alistair Burns Head of School of Psychiatry & Behavioural Sciences, Professor of Old Age Psychiatry, University of Manchester, have put together a programme of speakers from all over the country. Professor Arie and Professor Burns have worked together producing the programme for this national conference since the first conference took place in 1999.

The first day will begin with a key-note speech from Professor Ray Tallis, University of Manchester, looking at the philosophical aspects of dementia and consciousness. Following a range of talks on clinical topics, the day will conclude with a discussion on 'The best paper on dementias that I have read in the past year', with contributions from all speakers on day 1.

Professor Sube Banerjee, Professor of Mental Health and Ageing at the Institute of Psychiatry, London, will open the second day of the conference with a talk on the National Dementia Strategy: where are we now? Following talks on Psychotherapy and dementia and An overview of nursing care of people with dementia, Professor Roy Jones, Director of the Research Institute for the Care of Older People in Bath, will outline drugs which are currently in clinical trials, and look at the potential these may offer for future treatments.

In the afternoon of day 2, Professor Edzard Ernst, Laing Chair of Complementary Medicine from Peninsula Medical School, Exeter, will outline the place of complementary medicine in the treatment of patients with dementia, and then Professor Elaine Perry, Professor of Neurochemical Pathology, Institute for Ageing and Health, Newcastle University will talk about Plant power: the potential of phytotherapeuticals. These will be followed by a discussion of case histories and opinions on alternative treatments, which should make for an interesting debate.

The conference will provide participants with an update on ongoing clinical, research, organisational and policy developments that are taking place in the field of dementia, a forum to share and exchange views with eminent faculty speakers, a chance to look at progress in old age psychiatry and its service provision, and an update on the management of clinical conditions and practices associated with dementia, e.g. agitation and depression, as well as the chance to debate and discuss 'alternative therapies' for dementia.

Rebecca Linssen, Editor,
British Journal of Hospital Medicine.

For further information, or to book a place, go to www.mahealthcareevents.co.uk or phone 020 6501 6762

Recent Advances in the Treatment of Focal Dystonia: Update from the Dystonia Europe 2008 conference

The Dystonia Europe 2008 conference (October 17–19 in Hamburg, Germany) was the first major meeting for over 10 years with an exclusive focus on dystonia. It brought together experts from Europe and North America to discuss the latest developments in clinical practice and research.

The conference included a number of posters reviewing the latest findings from an extensive clinical development programme for Xeomin® in the treatment of focal dystonia. Xeomin® is a new formulation of botulinum neurotoxin type A that has recently been launched in the UK. Unlike existing therapies, Xeomin® is free from complexing proteins and can be stored at room temperature (<25°C) prior to reconstitution.[1]

The posters presented data demonstrating that Xeomin® is effective and well tolerated in the treatment of cervical dystonia and blepharospasm[2-4] and challenged the concept that complexing proteins may play a positive role in the stability and diffusion of botulinum toxin once injected.[5]

Comparable outcomes of Xeomin® (Botulinum neurotoxin type A) and Botox® in the treatment of focal dystonia

The results from two key studies were combined in a pooled analysis by Professor Jost from the Deutsche Klinik für Diagnostik in Wiesbaden, Germany.[2] The studies represented the two largest, randomised, double-blind, active-controlled clinical trials of botulinum neurotoxin conducted in patients with spasmodic torticollis[6] or blepharospasm.[7]

In both studies, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. Due to the differences in LD_{50} assays used by different manufactures, unit doses are specific to individual products and are not interchangeable. In these studies a conversion factor of 1:1 was used, such that if a patient was stable on 100 (Allergan) units of Botox® they were switched to 100 (Merz) units of Xeomin®. In the two studies a total of 384 patients received Botox® and 379 patients received Xeomin®.

In this combined analysis, Xeomin® was found to be equally as efficacious as Botox® across a number of physician and patient assessed parameters.[2]

- 72.8% of the investigators rated Xeomin® as 'good' or 'very good' (compared with 68.4% for Botox®) (Figure 1).
- 76.6% of patients indicated a moderate or marked improvement – including the complete abolition of symptoms – with Xeomin® treatment (compared with 72.0% with Botox® treatment) (Figure 2).
- 89.6% of patients indicated they had improved with Xeomin® treatment (compared with 85.8% with Botox® treatment) (Figure 2).
- The duration of treatment effect was almost identical in each treatment group (110 days with Xeomin® and 111 days with Botox®).
- The efficacy of Xeomin® and Botox® were shown to be statistically comparable.

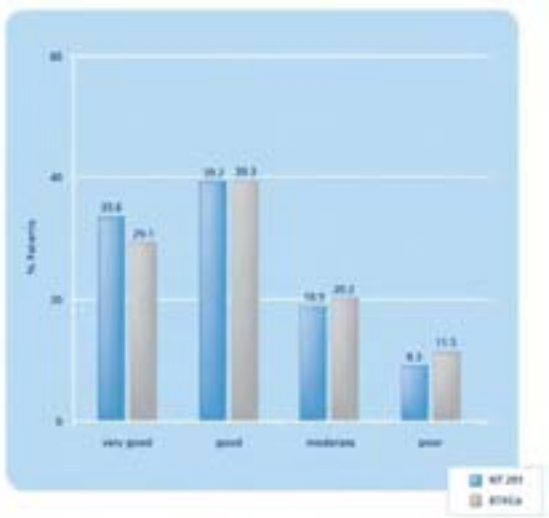


Figure 1: Investigators' global assessment of the efficacy of Xeomin® (NT 201) and Botox® (BTXCo) in focal dystonia (intention to treat analysis)[2]

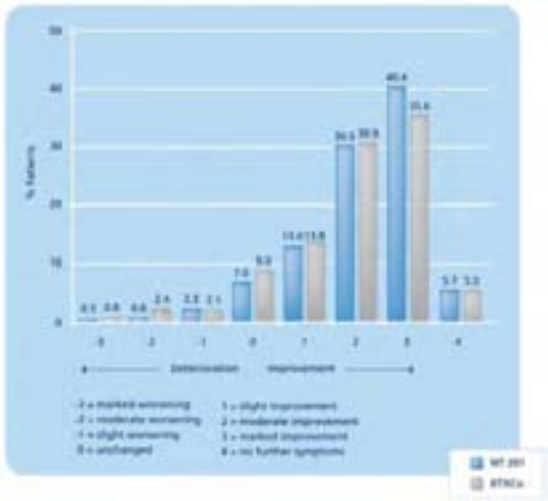


Figure 2: Patients' global assessment of the efficacy of XEOMIN® (NT 201) and Botox® (BTXCo) in focal dystonia (intention to treat analysis)[2]

Article publication sponsored by Merz Pharma UK Ltd.

Table 1: Mean change from baseline in BSDI scores three weeks after injection[3]

	Botox®		XEOMIN®	
	Number of patients	BSDI Score	Number of patients	BSDI Score
Male	35	-0.84	29	-0.81
Female	90	-0.82	100	-0.83
≤ 65 years	73	-0.79	63	-0.67
> 65 years	52	-0.86	66	-0.97

Table 2: Summary of adverse events reported with XEOMIN® (NT 201) and Botox® (BTXCo) in a pooled analysis of all studies.[4]

	NT 201 (n=539)	BTXCo (n=442)	Placebo (n=75)
Subjects with AEs (%):			
	144 (26.7)	115 (26.0)	17 (22.7)
Subjects with AEs (%) of intensity:			
Mild	98 (18.2)	81 (18.3)	13 (17.3)
Moderate	63 (11.7)	43 (9.7)	5 (6.7)
Severe	9 (1.7)	5 (1.1)	2 (2.7)
Subjects with SAEs (%):			
	13 (2.4)	12 (2.7)	1 (1.3)
Subjects with AEs (%) leading to:			
Withdrawal:	2 (0.4)	1 (0.2)	0 (0.0)
Death:	0 (0.0)	1 (0.2)	1 (1.3)

Values are n (%)
AE: Adverse events; SAE: Serious adverse events

In a further poster, Professor Roggenkämper et al from the University Eye Clinic in Bonn, Germany presented a sub-analysis of his original paper[7] comparing outcomes of blepharospasm patients switched from Botox® to Xeomin®.[3]

In this prospective, multicentre, randomised, double-blind, active-comparator study, 300 patients with blepharospasm were randomised to receive either Xeomin® or Botox® at a maximum respective dose of 50 units per eye.

Within the study protocol, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. As previously stated due to the differences in LD_{50} assays used by different manufactures, unit doses are specific to individual products and are not interchangeable. In this study, a conversion factor of 1:1 was used, such that if a patient was stable on 25 (Allergan) units of Botox® they were switched to 25 (Merz) units of Xeomin®.

The poster reviewed a sub-analysis of outcomes by patient gender and age (≤65 years and >65 years) using explorative statistics to confirm the previous findings of comparative efficacy between Xeomin® and Botox® in patients with blepharospasm.

The mean changes in the Blepharospasm Disability Index (BSDI) baseline scores were measured three weeks after injection. Patients that switched from an established dose of Botox® to a matched dose of Xeomin® were comparable between the groups with no relevant differences between the groups for age and gender being observed (Table 1).[3]

Clinical safety of Xeomin®: a meta-analysis

Xeomin® is indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults. Data presented in a poster by Dr Benecke from the Neurology Clinic in Rostock, Germany, presented the results of a meta-analysis of safety data from six controlled clinical trials (in patients with blepharospasm, cervical dystonia, post-stroke upper limb spasticity and healthy volunteers) involving 539 Xeomin®-treated subjects, 442 Botox®-treated subjects and 75 placebo-treated subjects.[4]

The meta-analysis demonstrated that (Table 2):[4]

- The incidence, type, and severity of adverse events (AEs) were similar in the Xeomin®-treated patients and the Botox®-treated patients.
- The incidence of serious AEs was low across all studies and all treatment groups.
- Most AEs reported with either Xeomin® or Botox® were mild or moderate in severity.
- The most common AEs (with an incidence ≥1%) in patients with cervical dystonia were dysphagia (a well-known injection site reaction), back and skeletal pain, and muscle weakness. The most common AEs in patients with blepharospasm were ptosis (another well-known injection site reaction), abnormal vision and back pain.
- Clinical laboratory evaluations showed no clinically-relevant safety signals.

The poster also included an analysis of the post-marketing surveillance from an estimated 62,000 patients treated with Xeomin® in clinical practice worldwide since the launch of Xeomin® in 2005.[4] The authors reported that no new safety concerns had been identified, and that the spontaneous reports identified from the surveillance either related to already well known safety concerns and/or were considered unlikely to be related to Xeomin® by the treating physician. The authors concluded that Xeomin® has a positive risk:benefit ratio, with a tolerability and safety profile comparable to Botox®.[4]

Complexing proteins and BTX-A preparations: therapeutic benefit?

The role and clinical significance of complexing proteins in first-generation neurotoxin products has been the subject of ongoing debate, with some researchers suggesting that they may be required for product stability, to prolong neurotoxin persistence, and inhibit neurotoxin diffusion into adjacent tissues.[8] Others point out that complexing proteins have no proven therapeutic benefits, and may actually play a role in the formation of antibodies that neutralise botulinum neurotoxin,[6,9] thereby potentially leading to clinical failure.[6]

In a poster at Dystonia Europe 2008, by Eisele et al, an analysis of the dissociation of the 900kDa neurotoxin complex at various pH values was presented. The researchers found that the 900kDa neurotoxin complex, which was stable at a pH of 6, rapidly separated into several fractions when the pH increased towards one of physiological value, releasing the 150kDa neurotoxin from the protein complex with a half-life of less than one minute.[5]

The authors compared the efficient release of the 150kDa neurotoxin following injection in physiological conditions with the extended time to onset of therapeutic effect, which is typically measured in days.[10] The authors conceded that complexing proteins may be required to stabilise first generation neurotoxin formulations. However, they argued that based on these data, the concept that complexing proteins may stabilise the neurotoxin once injected into the muscle[8] or inhibit its diffusion[11] must now be questioned.

The authors concluded that the rapid release of the 150kDa neurotoxin from the 900kDa complex under physiological conditions aids in the understanding of comparable clinical efficacy and safety demonstrated between Xeomin® and a botulinum complex containing complexing proteins.[5]

Article publication sponsored by Merz Pharma UK Ltd.

Product stability analysis

Unlike first generation neurotoxin complexes which require an effective cold-chain for storage and distribution, Xeomin® does not need to be refrigerated. An unopened vial can be safely transported and stored at room temperature conditions, of up to 25°C, for up to 3 years.[1] To validate these storage conditions Grein et al[12] performed a series of tests as defined in the ICH Q1A(R2) guideline on stability testing of drug products. Samples were stored at a range of temperatures including 5°C and 25°C and underwent a series of temperatures stress tests. Samples were tested in real time and under accelerated conditions using qualified incubators with narrow temperature tolerances.

The authors confirmed that there were no detrimental effects on the quality of Xeomin® across a range of temperature stress tests and that storage of Xeomin® at ambient conditions (25°C) for up to three years will not negatively affect its activity. The authors concluded that, in the case of Xeomin®, complexing proteins are not required to achieve product stability.[12]

KEY POINTS SUMMARY

Studies presented at Dystonia Europe 2008 (17–19 October 2008, Hamburg, Germany) have confirmed that:[2,3,4,5,12]

- Xeomin® is an effective treatment for the symptoms of spasmodic torticollis and blepharospasm
- Patients switched from their existing Botulinum toxin therapy to Xeomin® experienced comparable efficacy and tolerability
- Post-marketing surveillance of an estimated 62,000 patients worldwide has not identified any new safety concerns for Xeomin®
- Prior to reconstitution Xeomin® can be stored without refrigeration (≤25°) for up to three years

References

1. Xeomin® Summary of Product Characteristics. February 2008.
2. Jost WH, Grafe S, Comes G. *Efficacy of NT 201 in focal dystonia.* Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P31)
3. Roggenkämper P, Grafe S, Comes G. *Comparable outcomes of Xeomin® and Botox® in a prospective, randomized, double-blind, multicentre trial in patients suffering from blepharospasm.* Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P34)
4. Benecke R, Grafe S, Sassin I, Comes G. *Clinical safety of NT 201 (Xeomin®): a meta-analysis.* Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P33)
5. Eisele K-H, Taylor HV. *Dissociation of the 900 kDa neurotoxin complex for C. Botulinum under physiological conditions.* Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P09)
6. Benecke R, Jost WH, Kanovsky P et al. *A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia.* Neurology 2005;64:1949–51.
7. Roggenkämper P, Jost WH, Bihari K et al. *Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm.* J Neural Transm 2006;113:303–12.
8. Chen F, Kuziemko GM, Stevens RC. *Biophysical characterization of the stability of the 150-kilodalton botulinium toxin, the nontoxic component, and the 900-kilodalton botulinum toxin complex species.* Infect Immun 1998;66:2420–5.
9. Jankovic J, Vuong KD, Ahsan J. *Comparison of efficacy and immunogenicity of original versus current botulinium toxin in cervical dystonia.* Neurology 2003;60:1186–8.
10. Brin MF. *Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity.* Spasticity Study Group. Muscle Nerve 1997;6:s208–20.
11. Carruthers A, Carruthers J. *Toxins 99, new information about the botulinum neurotoxins.* Dermatol Surg 2000;26:174–6.
12. Grein S, Mander GJ, Taylor HV. *NT 201 is stable without refrigeration: Complexing proteins are not required for stability of botulinum neurotoxin type A preparations.* Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P32)

Xeomin® prescribing information can be found on page 39.

EDITOR'S CHOICE

Side-effects of anticonvulsants

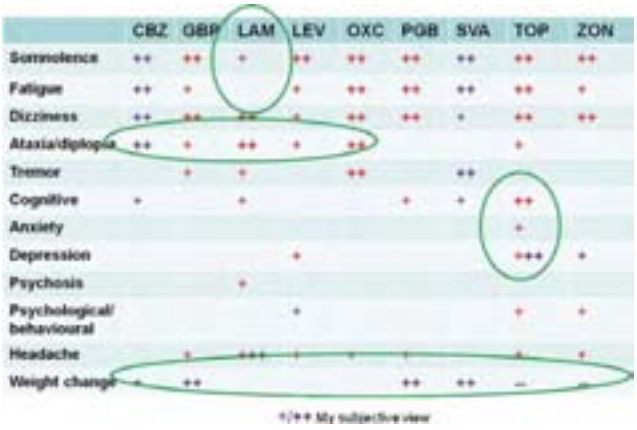
In this study the authors take a fairly rigorous view of the studies they are assessing and in the tradition of meta-analyses many less rigorous studies are excluded. They identified adverse effects which occurred more frequently (+) or significantly more frequently (++) in the treatment arm than in the placebo arm. I have added weight change and my impression of some older drugs in purple. The study supports the view that most drugs have a similar range of toxic effects but that lamotrigine is cleaner than the others with regard to cognitive effects. Sodium channel blocking drugs all seem to cause ataxia and diplopia – as is commonly recognised in clinical practice. Topiramate only caused a trend towards depression; it is more of a problem in my clinical experience. This is representative of the problem with this study, which is that the less common but severe side effects such as major depression and psychosis are not common enough to reach clinical significance in the studies used, so that the differences between drugs are under-emphasised. It is nevertheless interesting to see that the similarities are greater than the differences; perhaps we should just toss a coin. ***– MRAM***

Zaccara G, Gangemi PF and Cincotta M.

Central nervous system adverse effects of new anti-epileptic drugs. A meta-analysis of placebo- controlled studies.

SEIZURE

2008;17:405-21.



DEPRESSION: prevention of perinatal depression

If you identify depression in the last trimester of pregnancy, is there anything you can do to promote remission.. and avoid all the harmful consequences of poor bonding with the child? Well, intervention X reduces the prevalence of depression at 6 months after birth from 53% to 23%, and this effect is sustained for 12 months. Not bad. But what is remarkable is that agent X is not a drug, but cognitive behavioral therapy; more surprising still it is administered not to the affluent eloquent but to unselected mothers in rural Pakistan. People charmingly referred to as "Lady Health Workers" had a brief training and then administered one session of CBT every week for 4 weeks in the last month of pregnancy, three sessions in the first postnatal month, and nine 1-monthly sessions thereafter. The cost of this is not laid out. Sadly for the investigators, none of the infant-related outcomes differed significantly. Good on the Wellcome for funding work on an unglamorous condition, with negative pharmaceutical value, amongst overlooked peoples. ***– AJC***

Rahman A, Malik A, Sikander S, Roberts C, Creed F.

Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial.

LANCET

2008;372(9642):868-9.

HEADACHE: transformed migraine and analgesia

★★★ RECOMMENDED

Two point five percent of those with episodic migraine converted to chronic (transformed) migraine over a one year period. This report, which won the Harold G Wolff Lecture award for 2008, comes from the massive 120,000 population study (the American Migraine Prevalence and Prevention Study),

which followed 8219 (6.8%) migraineurs over five years. Of those migraineurs identified in 2005, 209 (2.5%) developed chronic migraine by 2006. This figure seems low, but the follow up was only one year, and this is likely to be at least one explanation. Unsurprisingly, higher baseline headache frequency was a risk factor for transforming to chronic migraine. Use of barbiturates and opiates were associated with increased risk of chronic migraine, even after adjusting for co-variates including baseline headache frequency and severity. Triptans were not associated with increased risk of transition from episodic to chronic migraine. Non-steroidal anti-inflammatory drugs (NSAIDs) had a variable effect, with a protective effect at low to moderate headache frequency, but an increased risk of transition to chronic migraine at high levels of monthly headaches. It is important that chronic migraine is now a recognised entity, as some previous classifications excluded those with daily headache from migraine; leaving them in a diagnostic and treatment limbo. What are the implications for us in the United Kingdom? Codeine use in headache patients is common, although barbiturate use is not. Other workers, particularly Diener, recognise opiate users as a refractory group of chronic migraineurs. It is often difficult to persuade these patients that the uncomfortable period of opiate withdrawal is worth it. Preventing this situation is important. The association between opiate use and chronic migraine is a strong argument for adequate and early prophylaxis to reduce the transformation from episodic to daily headache. There is still much work to be done on this, starting in primary care and emergency departments. ***– HAL***

Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB.

Acute Migraine Medications and Evolution From Episodic to Chronic Migraine: A Longitudinal Population-Based Study.

HEADACHE

2008;48:1157-68.

PARKINSON'S DISEASE: deciphering the dyskinesias

The development of levodopa induced dyskinesias (LIDs) is inevitable in patients with Parkinson's disease as they advance with their condition. The basis of these drug induced movement disorders has been debated for many years and has become a topic of even further interest since the description of graft induced dyskinesias in patients transplanted with fetal ventral mesencephalic tissue. One of the most popular hypotheses relates LIDs to a failure of dopamine storage in the remaining nigral dopaminergic terminals such that levodopa cannot be buffered and dopamine is released synchonously with each levodopa dose. Of late a second major theory has been evolving that relates LID to the mishandling of levodopa in 5HT nerve terminals in the striatum which then releases dopamine as a false transmitter again in an unregulated way. Finally others relate LIDs to the conversion of levodopa to dopamine in non neuronal cells which lack the capacity to regulate the release of the dopamine so formed. Indeed in the striatum the major determinant of dopaminergic levels at the synaptic level (outside of its release and thus synthesis) is its inactivation via dopamine transporters. Thus an abnormality in dopamine transporters, as would be the case for 5HT and non neuronal cellular release of dopamine, would cause dopamine to be released in an unregulated fashion. In other words the released dopamine cannot be taken up and thus there will be a pulsatile delivery of dopamine in time with the oral administration of the drug. This in turn will act via the postsynaptic dopamine receptors to effect downstream changes with the induction of long term LIDs. Lee et al have now added another part to the story using 6 hydroxydopamine lesioned rats. They show that once there is a greater than 60% denervation of the striatum, LIDs can be induced and this can be attributed to terminal sprouting from the intact nigrostriatal dopaminergic neurons. These sprouted terminals are capable of releasing dopamine but lack the necessary apparatus to transport and store it and thus contribute to LIDs. Thus once a threshold is passed when terminal sprouting with dopamine release is the dominant mode of synaptic dopamine delivery to the striatum, LIDs ensue. This paper contains an interesting series of experiments designed to confirm this observation and whilst not proven as the mode by which these dyskinesias occur in patients, does nevertheless help explain why LID's may occur. However the reality is, as the authors themselves acknowledge, that this is probably only one of several different mechanisms, all of which contribute to LID's and which in theory are all amenable to treatment with the expectation that LIDs can be better avoided and treated. ***– RAB***

Lee J, Zhu WM, Stanic D, Finkelstein DI, Horne MH, Henderson J, Lawrence AJ, O'Connor L, Tomas D, Drago J, Horne MK.

Sprouting of dopamine terminals and altered dopamine release and uptake in Parkinsonian dyskinaesia.

BRAIN

2008;131(Pt 6):1574-87. Epub 2008 May 16.

STROKE: Functional Electrical Stimulation can reduce unilateral spatial neglect after stroke

Spatial inattention or 'neglect' to the contralesional side is common in acute stroke. This deficit resolves in many cases but there are a small proportion of patients in whom the problem persists. Since severe and persistent spatial neglect prevents this sub-group of patients from regaining independence after stroke there is much interest in finding rehabilitation strategies to treat it. Unilateral spatial inattention is considered to be a syndrome because a variety of symptoms have been identified. This makes development of effective treatments that can be applied to very severely affected patients a challenging task and to date long-lasting treatments have been lacking. A proof of principle study reported recently in Neuropsychological Rehabilitation may be the start of a new lead in resolving this important clinical problem. Functional electrical stimulation (FES), a treatment that is normally applied to people with hemiparesis to activate muscles and bring about movement, was applied in this case to see if proprioceptive information on the contralesional side would improve patients' spatial awareness. The treatment was tested on four severely affected right hemisphere stroke patients and in three of them the treatment effects were remarkable. An A-B-A treatment-withdrawal design was used. Each patient was assessed weekly on a number of clinical tests over the baseline period of 4 weeks. A treatment phase immediately followed by a phase in which the stimulation was applied to the wrist/finger flexors and extensors of the forearm on the ipsilesional side (4 weeks). After that a second treatment phase stimulating the contralesional forearm (4 weeks) was delivered followed by a withdrawal phase (4 weeks) and a final follow up assessment 16 weeks after that. Thus the design allowed the effects of stimulation on spatial neglect to be separated from its effect on arousal by applying the electrical stimulation first to the arm on the ipsilesional side, before it was applied to the arm contralateral to the lesioned hemisphere. In three of the four patients the time series plots of performance remained consistently poor until the stimulation was applied to the contralesional side, then performance was greatly improved and was maintained through to the follow up assessment. The fourth patient did not change in performance throughout. The authors suggest that FES activates a proprioceptive map within the right parietal lobe whose level of activation is otherwise diminished by the lesion and that this both increases awareness of the contralesional side and stimulates functional interactions with the environment. This is a very simple treatment to apply in clinical practice and deserves further investigation to see if clinically meaningful results can be found in a larger study. ***– AJT***

Harding P, Riddoch MJ.

Functional Electrical Stimulation (FES) of the upper limb alleviates unilateral neglect: A case series analysis.

NEUROPSYCHOLOGICAL REHABILITATION

2008, DOI: 10.1080/09602010701852610

HEADACHE: olfactory hypersensitivity and migraine

This report gives another fascinating example of changes in the brain of patients with migraine. Visual hypersensitivity in migraine, and related physiological and blood flow changes, are well documented. Although less common, olfactory hypersensitivity both during and between migraine is established, and odours may trigger migraine. This study examined regional cerebral blood flow, in headache-free periods, in migraineurs with documented olfactory hypersensitivity. Regional cerebral blood flow in the left piriform cortex and antero-superior temporal gyrus was increased in 12 subjects in periods without odour stimulation, compared to 11 controls. During odour stimulation, migraineurs showed increased activation of frontal (left inferior and right middle frontal gyri), temporo-parietal regions, posterior cingulate gyrus and right locus coeruleus. These studies show a change in cerebral blood flow in these odour-sensitive migraineurs "at rest" and during activation. The authors point out that the study doesn't tell us the physiological mechanism of the changes. We don't know whether this represents a chronic change in cerebral flow consequent on migraine, or a primary change in the regulation of olfactory responses. It also doesn't tell us the mechanism of olfactory hallucinations as a migranous aura, which must be distinguished from ictal olfactory aura by the clinical setting, in particular their long duration. It does add to the evidence that there is something different both about how people with migraine process sensory input, and how their brain is between headaches. ***– HAL***

Demarquay G, Royet JP, Mick G, Ryvlin P.

Olfactory hypersensitivity in migraineurs: a H215O-PET study.

CEPHALALGIA

2008;28:1069-80.

PARKINSON'S DISEASE: dopamine and the sleeping brain

Proper sleep is important for the well being of us all and problems with inappropriate sleepiness during the day can be a feature of many neurological conditions, perhaps best described in Parkinson's disease (PD). In a recent issue of the Journal of Neuroscience two papers touch on the role of dopamine in this whole process. In the first of these papers Volkow et al study the effect of sleep deprivation on the dopaminergic systems in the striatum and thalamus using PET. These workers took healthy subjects and studied them after a night of normal restful sleep and again after a night of sleep deprivation. They looked at the dopaminergic system with two PET ligands- 11C-Cocaine which labels dopamine transporters and 11C raclopride (RAC) which labels mainly D2 receptors. They found that RAC (but not ^{11}C-Cocaine) binding in the striatum and thalamus was decreased after sleep deprivation and that this reduction correlated with the level of tiredness, fatigue and cognitive dysfunction. The decrease in RAC signal implies that sleep deprivation increases dopamine release as this PET ligand competes with endogenously released dopamine [or alternatively that sleep deprivation alters dopamine receptors directly]. This suggests that in an attempt to maintain arousal, in the face of lost sleep the dopaminergic system at these sites upregulates anyway, although proving that this is truly the case will require further work. However, Qu et al show that, in mice, modafinil induced wakefulness is dependent on dopamine receptors- D1 and D2 in particular. This is demonstrated using standard pharmacological studies as well as the D2 receptor deficient mice. These studies therefore tell us that dopaminergic stimulation underlies wakefulness, or at least contributes to it in the face of either sleep deprivation or the administration of modafinil. However, how this exactly plays out with other systems involved with sleep and wakefulness is not clear, nor why some diseases with dopaminergic loss, such as PD, cause problems with somnolence. Nevertheless it does show that this most basic of processes is complex and that dopamine is integral to its regulation. ***– RAB***

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, Ma J, Pradhan K, Tomasi D, Thanos PK, Ferré S, Jayne M.
Sleep deprivation decreases binding of [11C] raclopride to dopamine D2/D3 receptors in the human brain.
JOURNAL OF NEUROSCIENCE
2008;28:8454-61.

Qu WM, Huang ZL, Xu XH, Matsumoto N, Urade Y.
Dopaminergic D1 and D2 receptors are essential for the arousal effect of modafinil.
JOURNAL OF NEUROSCIENCE
2008;28:8462-9.

STROKE: thrombolysis after 3 hours….?

★★★ RECOMMENDED

Just when we had just got our heads around thrombolysis for those lucky 4% of patients who get to an appropriate place within three hours of their stroke, the goalposts may be moving. There have been several previous suggestions that intravenous tPa might be effective beyond the 3 hour window established by the NINDs study. But this is the most convincing evidence to date. The Safe Implementation of Treatments in Stroke (SITS) study is not a trial though. It is a systematic collection of real-world thrombolysis from approximately 700 centres in 300 countries. There is no control group. Instead, the SITS investigators have trawled through their database for the 664 patients who received their tPa between 3 and 4.5 hours after their stoke and compared their outcome with those 11,865 souls who got the juice within the conventional window. The bottom line is that there was no difference in the rate of symptomatic intracerebral haemorrhage (2·2% versus 1·6%); mortality at 3 months (12·7% versus 12·2%); or independence at 3 months (58·0% versus 56·3%). The trouble is that nearly 60% of the 3-4.5 hour group actually received their thrombolysis in the 20 minutes after the magic 3 hour cut-off, so the 4 hour tail-end charlies may not have benefited as much as first seems. One thing is for sure though…. If you have decided to thorombolyse within the 3 hours but the porters, radiographers and pharmacy conspire against you and the Cinderella hour has just past…. No worries. Give the IV push. It'll be alright…. ***– AJC***

Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, Roine RO, Toni D, Lees KR; for the SITS investigators.
Thrombolysis with alteplase 3-4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study.
THE LANCET
2008;372:1303-9.

EPILEPSY: predictive value of functional imaging

The trouble with studies looking into the selection of patients for epilepsy surgery, is that they are generally retrospective. They take a group of patients who have successfully undergone surgery and ask the question what criteria were the most reliable in selecting them. Of course, the problem with this approach is that it does not tell you how these factors relate to the patients who did not do well or to those who were rejected during the assessment. Perhaps that is not surprising, since one is never going to operate on patients whose investigations are not concordant, so the predictive value of non-concordance will never be known. Nevertheless, this pair of studies with the words "predictive value" in the title grabbed my attention. Do they truly address this question prospectively? What they did was to look at quite a large number of patients with refractory epilepsy, either with no clear structural abnormality on MRI or with such diffuse changes that further studies were needed to localise the onset of the epilepsy. These included intracranial EEG, magnetic source imaging (MSI), ictal SPECT and PET scans. Since MSI is a new technique, it was not considered in the process of deciding where to place intracranial electrodes. None of these tests is a gold standard, although 84% of patients with localised intracranial EEG did well with surgery. In predicting intracranial EEG, MSI had a positive predictive value of 90% (PET was 71%) and a negative predictive value of 42.3% (PET was 23.5%). SPECT was less sensitive or specific than PET. That MSI was most concordant with SEEG, no doubt reflecting the similarity of what the techniques measure. Combining PET and MSI or SPECT and MSI, improved predictive value, compared to MSI alone. So whilst the question of the true positive predictive value is perhaps not answerable, it is interesting that the most predictive test for intracranial EEG results in imaging negative patients in this study was MSI, an investigation, which is not widely available. However, when it came to predicting the outcome of epilepsy surgery in the second of the two papers, all three investigations performed similarly and again they supplemented each other. Reassuringly, when all the investigations were localising, the odds ratio for seizure freedom was 9.6 but the combination of MSI and PET seemed to be more predictive than MSI and ictal SPECT. So we come back to the view that the more tests which are concordant, the greater the predictive value and MSI is a useful new tool in the box whose role is increasingly defined and no doubt more centres will be looking to establish the technology. ***– MRAM***

Knowlton RC, Elgavish RA, Bartolucci A, Ojha B, Limdi N, Blount J, Burneo JG, Ver Hoef L, Paige L, Faught E, Kankirawatana P, Riley K, Kuzniecky R.
Functional imaging: II. Prediction of epilepsy surgery outcome.
ANN NEUROL
2008;64(1):35-41.

Knowlton RC, Elgavish RA, Limdi N, Bartolucci A, Ojha B, Blount J, Burneo JG, Ver Hoef L, Paige L, Faught E, Kankirawatana P, Riley K, Kuzniecky R.
Functional imaging: I. Relative predictive value of intracranial electroencephalography.
ANN NEUROL
2008;64(1):25-34.

Changes in the Editorial Board of Journal of Neurology

At the end of the year, there will be a change of Chief Editors in the Editorial Board of *the Journal of Neurology*. The long-time Board Member David Miller, London, will step down as Joint Chief Editor and will be succeeded by two new Chief-Editors, Dr Roger Barker, Cambridge, and Gérard Said, Paris. Prof Thomas Brandt, Munich, will continue to serve as Joint Chief-Editor of the Journal.

Roger Barker is Reader in Clinical Neuorscience at the University of Cambridge, UK, Honorary Consultant in Neurology at the Cambridge Centre for Brain Repair, and founding Editor of *ACNR*. He trained in neurology at Cambridge and at the

National Hospital in London. His main area of research is in neurodegenerative and movement disorders, in particular Parkinson's and Huntington's diseases.

The Journal of Neurology is an international peer-reviewed journal which officially represents the European Neurological Society (ENS) and provides a source for publishing original communications on clinical neurology and related basic research. *For more details visit www.springer.com*
Contact: Springer, Uschi Kidane,
T. +49 6221 487-8166,
E. uschi.kidane@springer.com

MRC grant successes for UCL

Professor Ken Smith who works in the Department of Neuroinflammation is one of the recipients of recently announced Medical Research Council awards, totalling £10.6 million.

UCL has been awarded eight out of the 20 available grants made by the MRC to fund research to develop better models of human disease – worth an estimated £4.2 million to the university.

The awards are one component of a strategic initiative to target bottlenecks in translational research, as part of the MRC's Translational Research Strategy, and Professor Smith's award of £761,372 is to develop therapies, and a strategy for their translation to treat early lesions in multiple sclerosis.

For more information contact: www.ion.ucl.ac.uk

Dr Sean O'Sullivan wins the Charles Symonds Prize

Dr Sean O' Sullivan from the Reta Lila Weston Institute of Neurological Studies has being awarded the Charles Symonds Prize by the Association of British Neurologists (ABN). This prize was awarded for the best platform presentation at the ABN Spring Meeting 2008. This prestigious and highly competitive award was based on research investigating clinical outcomes of progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). The study, using clinical data from pathologically-proven cases of PSP and MSA from the Queen Square Brain Bank, has been published in the journal 'Brain' in May 2008. Dr O'Sullivan said "This perspective of the whole disease course should help clinicians to anticipate patterns of disease progression in their management of people with PSP and MSA. Our findings may also furnish historical control data for future interventional studies".

For more information contact: www.ion.ucl.ac.uk

ABN Case Presentation Competition

Congratulations to Kate El Bouzidi who won the case presentation competition at the recent ABN Autumn meeting in Aviemore. Kate won the £100 prize from *ACNR* for her case presentation 'A case of reflex epilepsy associated with food-related stimuli.' Kate trained in Edinburgh and came across the case when she was a neurology house officer at the Department of Clinical Neurosciences at the Western General Hospital. She is now a core medical trainee and hopes to specialise in Infectious Diseases. The case will be reported in a future issue of *ACNR*.

Winners at the BMA Book Awards

Champagne corks have been popping at **Cambridge University Press**, following a string of successes at the 2008 BMA Book Awards. In the Neurology category, two titles garnered praise: Dizziness (Bronstein) was Highly Commended by the judges, whilst Frontotemporal Dementia Syndromes (Hodges) was also Commended.

The Press also scooped first prizes in Cardiology (Cardiac Arrest: The Science and Practice of Resuscitation Medicine, Paradis et al) and Mental Health (Handbook of Liaison Psychiatry, Lloyd and Guthrie).

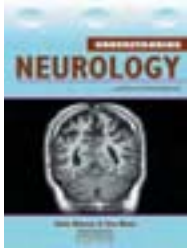
Richard Marley, publishing director for Life Sciences, Earth Sciences and Medicine, said, "I'm delighted by our success this year. These awards are a welcome and public endorsement of the quality of our content, as well as recognition of the dedication and effort that the authors and Press staff put into making these books happen."

For more information visit www.cambridge.org/medicine

Manson Publishing is honoured and pleased to announce that Understanding Neurology by John Greene and Ian Bone has won the Neurology prize in the BMA Medical Book Competition 2008. Richard Dawkins (right) is pictured presenting the award to Michael Manson.

The Judge commented, "Well-written with excellent diagrams and illustrating case studies. I particularly liked the visual field testing photos. Excellent - I would buy this and will recommend it …… a practical neurology textbook."

To order please contact Manson Publishing Ltd, 73 Corringham Road, London NW11 7DL. T. 020 8905 5150, F. 020 8201 9233, W. www.mansonpublishing.com



We have two copies of the book to give away to *ACNR* readers. Simply email your details to editorial@acnr.co.uk or write to ACNR, 1 The Lynch, Mere, Wiltshire BA12 6DQ by 12th December and the first two names out of the hat will win.

VIMPAT (lacosamide), a new epilepsy treatment for adults with partial onset seizures

Vimpat (lacosamide), a new adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older, has been launched in the UK.

The efficacy of VIMPAT® as adjunctive therapy at recommended doses (200mg/day, 400mg/day) was established in three multicentre, randomised, placebo-controlled clinical trials with a 12-week maintenance period. Overall the proportion of subjects with a 50% reduction in seizure frequency was 23%, 34%, and 40% for placebo, lacosamide 200mg/day and lacosamide 400mg/day, respectively. In addition, results from an open-label extension study demonstrate long-term retention on Vimpat.

Lacosamide was generally well tolerated when added to a broad range of AEDs, with no clinically relevant drug-to-drug interactions seen with the most commonly used AEDs.

For further information T. 01753 447 950, E. ian.weatherhead@ucb-group.com

MRI imaging leads pioneering neurological research

The MRC Cognition and Brain Sciences Unit (CBU) in Cambridge is an internationally renowned centre for research in the field of cognitive neurosciences. Its ground breaking studies into the brain function of vegetative state patients has provided invaluable insight into diagnosis pathways and the consequent care of the 'locked-in' patient.

The CBU is renowned for its clinical studies of vegetative state patients conducted in collaboration with colleagues at the Wolfson Brain Imaging Centre at Addenbrooke's Hospital which houses an identical MAGNETOM Trio MRI scanner from Siemens. Led by Dr Adrian Owen, the team recently looked into the brain activity during vegetative state, a condition where patients who emerge from a coma appear to be awake, but show no signs of conscious awareness. Traditionally, diagnosis for vegetative state is based on patient reaction to external stimuli i.e. noise or smell, but approximately 40% of patients are misdiagnosed as vegetative when in fact they may retain some degree of conscious awareness.

Using functional MRI (fMRI), a neuroimaging technique to study activity in the brain, researchers were able to test the neural

responses of patients diagnosed as vegetative. The findings suggested that residual cognitive capabilities were apparent in some cases and these allowed such patients to communicate their thoughts simply by modulating brain activity. When asked to process and respond to specific commands, the scanned images of apparent vegetative state patient's brains were indistinguishable from those of a healthy volunteer. The clinical studies took place at the Wolfson Brain Imaging Centre where patients with brain injuries are examined for evidence of preserved cognitive function.

For more information visit W. www.siemens.co.uk/healthcare

High-speed spectral acquisition with a single scan

Nikon Instruments' A1 series of confocal laser scanner systems has now been further enhanced by the launch of the A1Si spectral detector option which provides fast 32-channel spectral imaging with speeds of up to 16 fps at 512 x 64 pixels and real time spectral unmixing. This cell-friendly system offers the ultimate solution for reducing light exposure during multiprobe studies, capturing full spectral data in just one fast scan.

Fast fluorescence unmixing during image acquisition is possible, with a 512 x 512 pixel, 32-channel image unmixed in less than one second. Coupled with high-speed spectral imaging, a clearly resolved image with no crosstalk between closely overlapping fluorophore emissions can be created in real time.

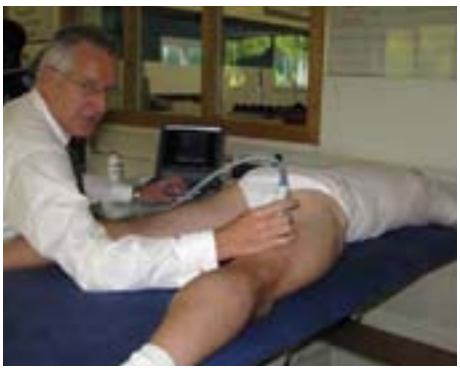
In addition, a new virtual filter function freely utilises the 32 channels, providing the flexibility to handle any new fluorescence probes. Desired spectral ranges can be selected and the total intensity of each range adjusted individually. Broader band spectral imaging is achieved on the A1Si, which requires only one pass of the laser to capture all the spectral data in the sample.

For further information contact Nikon Instruments Europe, T. 0208 247 1718, E. info@nikoninstruments.eu W. www.nikoninstruments.eu/a1/

MicroMaxx® ultrasound system helps injured Manchester City players back to fitness

Manchester City Football Club's doctor has chosen the SonoSite MicroMaxx® point-of-care ultrasound system to assess players' muscle injuries regularly and ensure that they are back on the field as quickly as possible.

"I liked the SonoSite MicroMaxx system because it is compact and portable," said Dr Mark Whitaker, the club doctor. "I thought it would be ideal in an environment like our treatment room. We use it mainly to help modify our rehabilitation programme; the pressure is on to keep the player fit and trained, and the MicroMaxx gives us the confidence to push players on if we can see that



there is no significant injury. Ultrasound imaging has allowed us to play some of our footballers in senior games that we would not have played before. The fact that we're looking at it in a scientific way gives the footballers huge reassurance too."

Dr Whitaker is involved in Manchester PCT's tier two musculoskeletal service and feels the potential for quick, early diagnosis of community patients using the MicroMaxx will ensure patients are treated in the most appropriate manner.

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

Donation of Brain Surgery System to 'Ukraine 3000'

Elekta recently announced a donation of Leksell Stereotactic System® for minimally invasive brain surgery to the International Charitable Foundation 'Ukraine 3000' for which Mrs Kateryna Yuschenko, wife of the President of Ukraine is the prime guardian. This donation was presented in the presence of Her Majesty Queen Silvia of Sweden, founder of the World Childhood Foundation. The system will be used for treating a wide range of brain disorders at one of the leading neurosurgery hospitals in Ukraine.

Elekta is a human care company pioneering significant innovations and clinical solutions for treating cancer and brain disorders. The Leksell Stereotactic System is a system for advanced stereotactic neurosurgery, a minimally invasive form of surgery which allows the surgeon to take biopsies and treat brain disorders with the highest precision and minimal trauma to the patient. It has become the system of choice in the whole world for treating functional diseases, for example Parkinson's disease.

The total value of the donated system, which also includes training at one of Elekta's renowned European reference sites, is around EUR 70,000.

For more information
T. +46 8 587 254 27,
E. lena.hoglund@elekta.com

Elekta extends its line of Stereotactic Treatment Solutions at 2008 Congress of Neurological Surgeons Annual Meeting

Elekta recently introduced Extend™*, a new stereotactic treatment programme that lets neurosurgeons and radiation oncologists apply the power and precision of Gamma Knife® surgery to an even broader class of targets in the head and neck.

For more than twenty years, Leksell Gamma Knife surgery has been the gold standard in intracranial radiosurgery. With its new relocatable frame and support for fractionated treatments, the Extend program now provides the ability to treat large or critically located targets in the head and neck that were previously untreatable with Gamma Knife surgery. The result is an exciting crossover solution for neuro-oncology that combines Elekta's recognised excellence in stereotaxy with its proven expertise in radiation medicine.

"When faced with lesions that are too large or too critically located to be safely treated in a single session, Extend enables clinicians to divide the radiation dose over multiple treatments," says Mark Symons, Senior Vice President, Stereotactic Business Unit. "It also includes the most precise non-invasive fixation option available, allowing both neurosurgeons and radiation oncologists to treat more patients with greater confidence."

For further information E. Joanne.Latimer@elekta.com

Carl Zeiss introduces Axio Scope.A1

Life science research and routine applications will benefit from the flexibility and adaptability of the Axio Scope.A1 microscope from Carl Zeiss. The modular design allows users to configure a microscope to their precise needs, safe in the knowledge that changes and upgrades can be implemented easily and quickly if demands change.

The Axio Scope.A1 is ideal for pathology, histology, cytology, microbiology, environmental research, molecular biology, plant physiology, developmental biology or genetics laboratories. Users have a choice of 23 stands, LED or halogen illumination, a retro-fittable fluorescence system, phase contrast, differential interference contrast (DIC) and the PlasDIC technique developed by Carl Zeiss, available in an upright routine microscope for the first time.

The LEDs for fluorescence applications are fully integrated into the stand and offer a long service life with reduced running costs, excellent image contrast and ease of use. The newly-developed Ergo-stage can be locked along the y axis in exactly the position that a user finds most comfortable and convenient and an extended specimen area is adjustable for specimen heights of up to 110 mm. If one of the optional Vario stands is chosen, larger specimens of up to 380mm may be examined.

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

Image capture at two wavelengths simultaneously

Faster, simpler imaging of cellular events is now possible as Nikon's Eclipse Ti Series inverted microscopes can capture images at two different wavelengths simultaneously, using dual cameras. Accelerating image acquisition while maintaining full frame resolution, the system is ideal for FRET and the capture of rapid dynamic cellular events using calcium or other ion-targeted probes, ratio probes, dual emission ratiometric dyes etc.

The two cameras are positioned on the Eclipse Ti's back and side ports. Perfect registration between the two cameras is assured on installation to ensure that no information is lost during imaging. No further realignment or specialised alignment software is required Even when the intensity difference between wavelengths is large, high-quality images can be captured by adjusting camera sensitivity for each wavelength.

Nikon has partnered with Andor to offer their full range of high-performance iXon+ and Luca EMCCD cameras. The IxonEM+ 897 back-illuminated EMCCD camera offers high sensitivity, low noise and rapid frame rates giving distinct speed advantages in FRET applications. The cameras are optimised for use with Nikon's dedicated NIS-Elements software for image capture, processing and analysis. Unified integrated control of microscope and cameras offers significant benefits for cutting-edge live cell research. NIS-Elements C for confocal microscope applications includes FRET analysis software as standard.

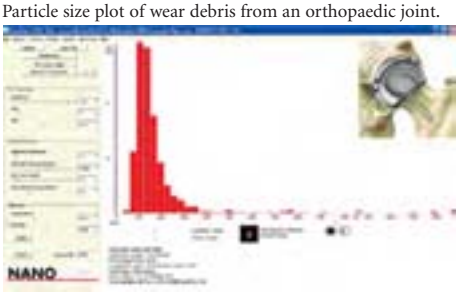
For further information contact Nikon Instruments Europe, T. 0208 247 1718,
E. info@nikoninstruments.eu
W. www.nikoninstruments.eu/a1/

NanoSight speeds Leeds University's characterisation of wear debris in orthopaedic implants

NanoSight Limited, the nanoparticle characterisation company, has announced that the University of Leeds is committed to the use of their Nanoparticle Tracking Analysis system for the study of wear debris generated in orthopaedic implants.

Dr Joanne Tipper of the Institute of Molecular and Cellular Biology studies nanoparticle sized polymer debris, specifically polyethylene generated first in vitro (to prove its presence) and then in vivo (from tissue from around failed hip replacements). The objective was first to characterise/size the particles and then to consider their bioactivity and effect on cell responses.

Particle size plot of wear debris from an orthopaedic joint.



Dr Tipper has made measurements on different materials used for implants (metal-metal, ceramic-ceramic and polymer-polymer). She has had good results on model metal and ceramic particle systems. The metal nanoparticle debris are typically in the range of 20-80nm which is particularly suited to NTA when compared to light scattering methods. The NTA results compare extremely well with high resolution FEG-SEM, and these particles compare well with clinically generated wear debris. NTA has proven to be much easier to use, requiring minimal sample preparation time compared to SEM and then providing results in minutes. When studying polymers, NTA produced excellent results for polyethylene particles in the 100-800nm range, again when compared to FEG-SEM.

For more information visit W. www.nanosight.co.uk

Anaesthetic team evaluation reveals the Lightman® detects inaccurate Pulse Oximeter probes

The Electrode Company Ltd, inventors of the world's first patient in adaptive noise cancellation in pulse oximetry produce the Lightman®. This market-leading pulse oximeter sensor tester was the subject of a successful presentation at the summer scientific meeting of the Anaesthetic Research Society in June.

The presentation was made by Dr C Dunstan, on behalf of the team from The Anaesthetic Departments of the University Hospital Wales and the Clinical School of the Royal Gwent Hospital, Newport. In it they concluded that 'the Lightman® can detect the faulty probes' and 'facilitate the removal of faulty probes from the clinical environment.'

The Lightman® is designed to detect pulse oximeter sensor accuracy. The Anaesthetic Team decided to evaluate its predictions against a blood gas analyser. The evaluation showed that sensor errors are larger at lower saturation levels. Blood gas analysis confirmed errors of up to 9%. A lively Q&A session followed the presentation which also showed that in a previous hospital survey at Newport, the Lightman® found 11% of the probes to be significantly inaccurate leading to 'possibly serious consequences' or 'unnecessary and perhaps harmful intervention'.

For more information T. 01291 650279, W. www.electro.co.uk

'Oar' inspiring stroke campaign launched

Siemens, high performance partner of GB Rowing, and The Stroke Association have launched the Stroke for Stroke campaign 2008 aiming to highlight the positive benefits of regular exercise and help educate and inform the public about strokes and stroke prevention. In 2007 the initiative raised £40,000.

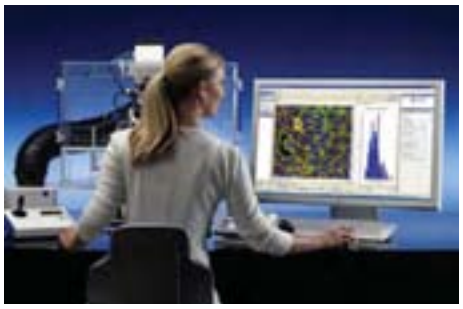
"Each year an estimated 150,000 people in the UK will have a stroke. This puts a big pressure on the NHS in terms of identifying symptoms quickly so that an accurate course of treatment can be prescribed. Prevention has to go hand in hand with expanding the provision of diagnostic and treatment facilities available to patients. Access to rapid CT scanning upon admission to hospital is essential to diagnosis and determination of treatment. This is especially important as some patients may benefit from a reperfusion therapy that is only currently administered within a three hour window from the onset of symptoms. This treatment not only helps to save lives, it can also dramatically improve the quality of life to survivors of this condition," states Peter Harrison, Director of Imaging & Oncology Systems at Siemens Healthcare.

Siemens and GB Rowing have launched the Siemens Stroke for Stroke campaign 2008.

Four time Olympic gold medallist, Sir Matthew Pinsent CBE is backing the campaign.

For more information visit W. www.siemens.co.uk/healthcare

Automatic High-Content Image Analysis Simplifies Cell Research



New software from Carl Zeiss automatically extracts biologically relevant data from micrographs by combining high-resolution fluorescence imaging and complex image analysis. Developed with the high content screening specialist, Cellomics®, the AxioVision ASSAYbuilder module inherits 15 years of experience in the field of High-Content Analysis (HCA) to offer the most reliable method of high content analysis and screening.

ASSAYbuilder supports the examination of processes in cells, between cells or in small organisms and will be especially useful in studies such as apoptosis, cytotoxicity, molecule localisation and translocation, cell differentiation and proliferation, GFP expression, and GPCR signal pathways. For example, users can analyse the position of the cytoskeleton or determine the proportion of living and dead cells in a sample. Furthermore, it allows the characterisation of cell cultures, the identification of new cellular starting points for the development of future medication, and the identification of lead substances in small or medium screenings in pharmaceutical research.

The ease-of-use means that researchers can concentrate on efficiently planning further experiments and publishing their results rather than having to become expert at the fundamentals of image analysis. However, the software module is sufficiently powerful to cope with even highly sophisticated requirements, such as subpopulation analyses.

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

COPAXONE® (glatiramer acetate)

PRE-FILLED SYRINGE PRESCRIBING INFORMATION

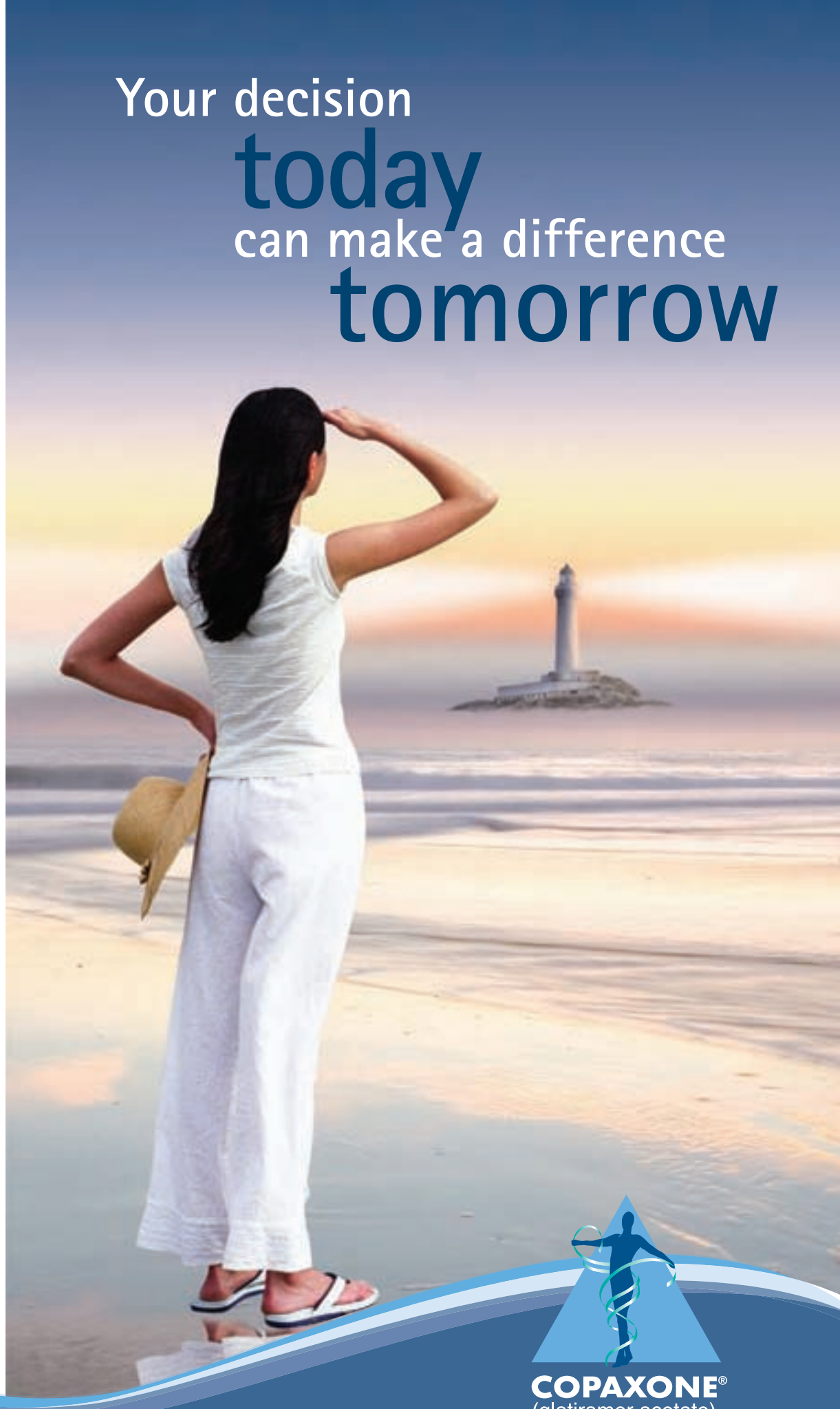
Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Reduction of frequency of relapses in relapsing-remitting multiple sclerosis in ambulatory patients who have had at least two relapses in the preceding two years before initiation of therapy. **Dosage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

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

Reference: Ford C. *et al. Multiple Sclerosis* 2006; 12: 309-320.

Date of preparation: June 2008 Code: C0807/428e

Your decision today can make a difference tomorrow



COPAXONE®
(glatiramer acetate)

Long-term active

TEVA

sanofi aventis
Because health matters