

ACNR

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ADVANCES IN CLINICAL NEUROSCIENCE & REHABILITATION

In this issue

Iracema Leroi – Cognitive and Behavioural Complications of Parkinson's Disease

Christopher R Sibley, Janine Scholefield and Matthew JA Wood

– RNA Interference and Neurological Disorders

Paediatric Neurology – Rachel Howells

– Headache in Childhood and Adolescence

Clinical Dilemmas in Neuropsychiatry – Valerie Voon

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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 and with or without levodopa. **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. **Overdose:** Symptoms reported following rasagiline overdose (3-100mg) included dysphoria, hypomania, hypertensive crisis and serotonin syndrome. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Do not use in patients with severe hepatic impairment. 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 (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), tricyclic and tetracyclic antidepressants, and MAO inhibitors. Cases of serotonin syndrome have been reported post-marketing

in patients treated concomitantly with antidepressants/SNRIs and rasagiline. 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. Cases of elevated blood pressure have been reported in the post-marketing period, including one report of hypertensive crisis associated with the ingestion of unknown amounts of tyramine. **Undesirable effects in clinical trials:** **Monotherapy:** >1%: headache, influenza, skin carcinoma, leucopenia, allergy, depression, hallucinations, conjunctivitis, vertigo, angina pectoris, rhinitis, flatulence, dermatitis, musculoskeletal pain, neck pain, arthritis, urinary urgency, fever, malaise. <1%: decreased appetite, cerebrovascular accident, myocardial infarction, vesiculobullous rash. **Adjunct therapy:** >1%: dyskinesia, decreased appetite, hallucinations, abnormal dreams, dystonia, carpal tunnel syndrome, balance disorder, orthostatic hypotension, abdominal pain, constipation, nausea and vomiting, dry mouth, rash, arthralgia, neck pain, decreased weight, fall. <1%: skin melanoma, confusion, cerebrovascular accident, angina pectoris. **Please refer to the SmPC for the rates of adverse events.** **Basic NHS Price:** Azilect® (tablets) 1mg x 28 £70.72 **Legal category:**

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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.

References:

1. Olanow CW et al. N Engl J Med 2009;361:1268-78.
2. Parkinson Study Group. Arch Neurol 2002;59:1937-1943.
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Professor Nils Erik Gilhus, Norway: Professor of Neurology at the University of Bergen and Haukeland University Hospital.

Alastair Compston wins KJ Zülch Prize

Professor Alastair Compston, Head of the Department of Clinical Neurosciences at the University of Cambridge, has been awarded the KJ Zülch Prize for his contributions to research on multiple sclerosis. Professor Compston received the award with his co-recipient, Professor Hans Lassman from the University of Vienna, for their 'internationally outstanding achievements in basic neurological research'. The prize, often recognised as one of the most prestigious in the field of neuroscience, is given annually on behalf of the Gertrud Reemtsma Foundation by the Max Planck Society for the Advancement of Science. For over 30 years, Professor Compston has been researching the causes and treatments of multiple sclerosis. His current research focuses on using the leukaemia drug alemtuzumab to treat multiple sclerosis.



WHO acknowledges charity's work

National Society for Epilepsy (NSE) neurologists are delighted their London base has been redesignated as a World Health Organisation (WHO) collaborating centre for research and training in neurosciences. NSE professor, Ley Sander, also a director for the department of clinical and experimental epilepsy at University College London's (UCL) Institute of Neurology, said: "We are so pleased that our work at UCL which involves research, training and education and information dissemination is recognised and we are delighted to continue to be a WHO collaborating centre." NSE's research programme is closely allied to the medical services it provides at its Epilepsy Centre in Chalfont St Peter, Buckinghamshire. These services are run in collaboration with UCL to offer an unsurpassed level of care which also means that important findings can quickly be translated into clinical practice.

For more information contact: Tel. 01494 601404, Email: amanda.cleaver@epilepsysociety.org.uk

Merck Serono Announces Winner of the Real MS: Your Story Competition

Merck Serono has announced the winner of the Real MS: Your Story international script concept competition to be Sarah Mead from the UK, as selected by a judging panel. The winning script, titled 'It's a marathon, not a sprint...', will now be brought to the screen in an international short film directed by award-winning Director, Robin Sheppard, to show the world that life with MS can be redefined in a positive and fulfilling way. Real MS: Your Story is the first element of an international campaign that aims to raise global awareness of MS and demonstrate how life can and could be improved for people living with MS, and their families and carers. The judging panel included global film and MS experts who selected Sarah's script concept from over 120 entries. Working with Robin Sheppard, Sarah will now see her work brought to life as a short film.

To find out more about the campaign and life with MS, visit www.realmsvoices.com

Dementia research receives £1.5 million boost

Research that could take scientists a step closer to discovering the cause of Alzheimer's and a study on how to improve care for people with dementia in hospitals are two of nine research projects that have been announced. The projects have been made possible following a £1.5 million grant jointly from Alzheimer's Society and the Bupa Foundation. Top scientists in the UK and Australia are being funded as part of an exciting new partnership between the two charities to boost research into the prevention, diagnosis and treatment of dementia. One of the projects being funded is a study by Dr Armit Mudher into the role of the tau protein in Alzheimer's disease. Healthy nerve cells produce tau but in Alzheimer's, an abnormal form of the protein is produced which does not function correctly. In her most recent research, Dr Mudher - from the University of Southampton - tested the effect of Lithium on tau, a drug commonly used for bipolar disorder. She found that Lithium not only protects cells from the effects of tau, but also causes the abnormal tau to accumulate in rounded clumps which are then less likely to cause damage to the cell. Dr Mudher will use high powered microscopy and biochemical techniques to find out exactly what the clumps are made of, how they are formed, whether they protect nerve cells and whether any other means can be used to produce them.

For more information contact: Tel. 0207 423 3595, Email: joanne.beaney@alzheimers.org.uk

ENS elects new member to its Executive Committee

Prof Kailash P Bhatia has been elected as new member of the ENS Executive Committee. Prof Bhatia is a Professor of Clinical Neurology in the Sobell Department of Movement Neuroscience at the Institute of Neurology, UCL, Queen Square, London and an Honorary Consultant Neurologist at the affiliated National Hospital for Neurology, Queen Square.

For more information see www.ensinfo.org



Image: Peter Fraser

*When you've got MS, just opening
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MS can make simple, everyday tasks difficult or impossible. Adding Sativex to existing spasticity treatment can improve symptoms like stiffness and spasm, helping to make daily life easier for people with MS.

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Instead of leaving the Sativex prescribing information at the foot of the page, we've put it where you can't miss it. Please take a look. After all, these are the crucial details that will help you decide if Sativex can help your MS patients.

Sativex® Oromucosal Spray Prescribing Information (refer to full Summary of Product Characteristics (SmPC) before prescribing). Presentation: 1mL contains: 38-44mg and 35-42mg of two extracts from *Cannabis sativa* L., (Cannabis leaf and flower) corresponding to 27mg delta-9-tetrahydrocannabinol (THC) and 25mg cannabidiol (CBD). Each 100 microlitre spray contains: 2.7mg THC and 2.5mg CBD. **Indication(s):** as add-on treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy. **Posology and method of administration:** oromucosal use only. Treatment must be initiated and supervised by a physician with specialist expertise in MS. Direct spray at different sites on the oromucosal surface, changing site for each use of product. May take up to 2 weeks to find optimal dose, review response after 4 weeks of treatment. Re-evaluate long term treatment periodically.

Adults: titration period necessary; number/timing of sprays will vary between patients. Number of sprays increased daily according to SmPC table, up to maximum of 12 sprays per day with minimum 15 minutes between sprays. **Children and adolescents:** not recommended. **Elderly:** no specific studies but CNS side effects may be more likely (see Warnings and precautions) **Significant hepatic or renal impairment:** no specific studies but effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation recommended. **Contra-indications:** hypersensitivity to cannabinoids or excipients. Breast feeding. Known/suspected history or family history of schizophrenia/other psychotic illness. History of severe personality disorder/other significant psychiatric disorder other than depression due to underlying condition. **Warnings and precautions:** not recommended in patients with serious cardiovascular disease. Caution in patients with history of epilepsy/recurrent seizures. THC and CBD are metabolised in the liver. Several THC metabolites may be psychoactive. Contains approx. 50% v/v ethanol. Risk of falls if spasticity/muscle strength no longer sufficient to maintain posture/gait. CNS side effects e.g. dizziness, somnolence could impact personal safety, e.g. hot food and drink preparation. Theoretical risk of additive effect with muscle-relaxing agents, not seen in clinical trials but warn patients risk of falls may increase. No effect seen on fertility but cannabinoids shown to affect spermatogenesis in animals. Female patients of child-bearing potential/male patients with a partner of child-bearing potential should use reliable contraception. Patients with a history of substance abuse may be more prone to abuse Sativex. Withdrawal symptoms following abrupt withdrawal of long-term Sativex are likely to be limited to transient disturbances of sleep, emotion or appetite. No increase in daily dosage observed in long-term use; self-reported levels of 'intoxication' low; dependence on Sativex unlikely. **Interactions:** no clinically apparent

drug-drug interactions seen. Co-administration with food results in mean increase in C_{max} , AUC and half-life (increase less than between-subject variability in these parameters). Concomitant ketoconazole increases C_{max} and AUC of THC (and primary metabolite) and CBD. Increase less than between-subject variability. Risk of additive sedation and muscle relaxing effects with hypnotics, sedatives and drugs with sedating effects. **Pregnancy and lactation:** do not use in pregnancy unless benefit outweighs potential risks. Do not use if breast feeding. Insufficient experience of effects on reproduction - use reliable contraception during therapy and for 3 months after discontinuation. **Effects on ability to drive and use machines:** do not drive, operate machinery or engage in any hazardous activity if experiencing significant CNS side effects; warn patients may cause loss of consciousness. **Side effects:** very common - dizziness, fatigue; common - anorexia, decreased or increased appetite, depression, disorientation, dissociation, euphoria, amnesia, balance disorder, disturbance in attention, dysarthria, dysgeusia, lethargy, memory impairment, somnolence, blurred vision, vertigo, constipation, diarrhoea, dry mouth, glossodynia, mouth ulceration, nausea, oral discomfort/pain, vomiting, application site pain, asthenia, feeling abnormal/ drunk, malaise, fall; uncommon - hallucination, illusion, paranoia, suicidal ideation, delusional perception, syncope, palpitations, tachycardia, hypertension, pharyngitis, throat irritation, upper abdominal pain, oral mucosal disorders e.g. discolouration, exfoliation, stomatitis, tooth discolouration, application site irritation; unknown frequency - psychiatric symptoms e.g. anxiety and mood changes, transient psychotic reactions, possible leukoplakia (unconfirmed); inspect oral mucosa regularly in long term use.



Prescribers should consult the SmPC for further information on side effects. **Overdose:** symptomatic and supportive treatment required. **Special precautions for storage:** refrigerate (2 to 8°C); once opened refrigeration is unnecessary but do not store above 25°C. **Legal Category:** POM **Package quantities and basic NHS costs:** 3 x 10mL £375.00. **MA holder:** GW Pharma Ltd, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ **MA number(s):** PL 18024/0009 **Further information available from:** Bayer Schering Pharma, Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** March 2010.

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In this issue of the ACNR we have two different accounts on the problems of treating Parkinson's disease with dopaminergic medication. In the first, Ira Leroi discusses the adverse neuropsychiatric effects of dopaminergic therapy in Parkinson's disease, whilst Valerie Voon discusses a specific scenario in her contribution to our Neuropsychiatry Series. In both articles the problems of making the diagnosis are highlighted as such drug induced changes in behaviour may not be recognised as being abnormal or therapy related by the patient and family. Of course making the diagnosis is one thing, what you do next, another, as the patients obviously need their dopaminergic medication for control of their motor symptoms. Both articles help us negotiate this tricky and emerging area of therapeutics in Parkinson's disease.

RNA interference (RNAi) has become a hot topic in the world of medicine as the potential to use this approach to silence the products of bad genes has massive implications for treating certain disorders- e.g. mutant huntingtin in Huntington's Disease. In our review article from the laboratory of Matthew Wood we are guided through the complexities of this topic and how it may be useful for treating disease. This review is easy to read, and gives a realistic perspective on the strengths and problems of using RNAi as a therapeutic approach and how it will impact on clinical medicine in the future.

Rachel Howells is the author of the next article in our series on Paediatric Neurology and takes as her theme the problem of headache in childhood and adolescence. In this article we learn that much of what we see in the adult clinic with respect to headache also applies to younger patients, but that there are also important differences, especially with respect to how migraine may present. This is a well crafted review that will be of great value to those faced with the young person with bad heads.

The role of the basal ganglia has vexed neuroscientists and neurologists for many years and in the latest in our series on Motor Control, Pietro Mazzoni and Martyn Bracewell discuss this thorny issue. In their article, they explain how our thinking has evolved since the work of David Marsden and how understanding the role of the basal ganglia in motor control gives insights into their greater role in action selection and reward.

Andrew Lerner in his latest short piece on neurology and literature discusses the use of the word megrim. This word is perhaps not known by most, but has been used in a variety of different ways by authors over the years as Andrew reveals through his close reading of many texts.

In a new series, we discuss the relationship between art, artists and neurology. In the first of this series we discuss the work of Willem de Kooning, who late in life developed a dementing illness. This changed his productivity and also raised questions as to the value of what he was painting. We hope that you enjoy this new series.

Finally, we have our usual collection of book, conference and journal reviews which cover a range of topics including neuroimmunology, epilepsy, functional imaging, neurodegeneration and rating scales and a trial for non-epileptic attacks. ♦



Roger Barker, Co-Editor.

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

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

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PRESCRIBING INFORMATION (Please consult the Summary of Product Characteristics (SPC) before prescribing.) **Vimpat® Lacosamide Active Ingredient:** Tablets: lacosamide 50 mg, 100 mg, 150 mg and 200 mg. Syrup: lacosamide 15 mg/ml. **Solution for infusion:** lacosamide 10 mg/ml. **Indication:** 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 for patients with severe renal impairment and patients with end-stage renal disease (see SPC). 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. Monitor patients for signs of suicidal ideation and behaviours. Advise patients and carers to seek medical advice should such signs emerge. **Interactions:** Prolongations in PR interval with lacosamide have been observed in clinical studies. Use with caution in patients treated with products associated with PR prolongation and those treated with class I antiarrhythmic drugs. Strong enzyme inducers such as rifampicin or St John's Wort may moderately reduce the systemic exposure of lacosamide. No significant effect on plasma concentrations of carbamazepine and valproic acid. Lacosamide plasma concentrations were not affected by carbamazepine and valproic acid. No clinically relevant interaction with ethinylestradiol and levonorgestrel. No effect on pharmacokinetics of digoxin. **Pregnancy and Lactation:** Should not be used during pregnancy. For precautionary measures, breast feeding should be discontinued during treatment with lacosamide. **Driving etc.:** Patients are advised not to drive a car or operate other potentially hazardous machinery until they are familiar with the effects of Vimpat on their ability to perform such activities. **Adverse Effects:** Very common (≥10%): Dizziness, headache, diplopia, nausea. Common (between 1%-10%): Depression, balance disorder, abnormal coordination,

memory impairment, cognitive disorder, somnolence, tremor, nystagmus, blurred vision, vertigo, vomiting, constipation, flatulence, pruritus, gait disturbance, asthenia, fatigue, fall, skin laceration. Adverse reactions associated with PR prolongation may occur. Consult SPC in relation to other side effects. **Pharmaceutical Precautions:** Tablets: None. Syrup: Do not store above 30°C. Use within 4 weeks of first opening. **Solution for infusion:** Do not store above 25°C. Use immediately. **Legal Category:** POM. **Marketing Authorisation Number(s):** 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: £10.81; 100 mg x 14 tabs: £21.62; 100 mg x 56 tabs: £86.50; 150 mg x 14 tabs: £32.44; 150 mg x 56 tabs: £129.74; 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. **Marketing Authorisation Holder:** UCB Pharma SA, Allée de la Recherche 60, B-1070 Bruxelles, Belgium. **Further information is available from:** UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 01753 534655. Fax: 01753 536632. Email: medicalinformationuk@ucb.com. **Date of Revision:** 01/2010 (10VPE0010). Vimpat is a registered trademark. **References:** 1. Vimpat Summary of Product Characteristics, 2010. 2. Beyreuther BK et al. CNS Drug Rev 2007; 13(1): 21-42. 3. UCB Data on file. **Date of preparation:** June 2010. 10VPE0137



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CONTENTS

NOVEMBER/DECEMBER 2010

03 Awards & Appointments

06 From the Editor...

Review Article

10 Cognitive and Behavioural Complications of Parkinson's Disease

Iracema Leroi

Neurological literature

16 Headache (Part 7): Migraine

Andrew J Larner

Review Article

17 RNA Interference and Neurological Disorders

Christopher R Sibley, Janine Scholefield and Matthew JA Wood

Motor Control Series

22 The Persistent Mystery of the Basal Ganglia's Contribution to Motor Control

Pietro Mazzoni and Martyn Bracewell

Paediatric Neurology

27 Headache in Childhood and Adolescence

Rachel Howells

Neurology in Art

30 Neurology And Art: Willem De Kooning

Sebastian Barker and Roger Barker

Clinical Dilemmas in Neuropsychiatry

32 When is an Impulse Control Disorder in Parkinson's Disease a Problem?

Valerie Voon

Association of British Neurologist Trainees

34 The ABN Fellowship Scheme: a new opportunity for neurology trainees

Biba Stanton

Book Reviews

35 Immune-Mediated Neuromuscular Diseases;
Measurement Scales Used in Elderly Care;
A Compendium of Tests, Scales, and Questionnaires The Practitioner's
Guide to Measuring Outcomes after Acquired Brain Impairment

Regulars

36 Journal Reviews

40 Conference News

43 Events Diary

47 News Review

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The Poseidon statue and fountain is the most well-known landmark of Gothenburg. © Kjell Holmner/Gothenburg & Co.

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APO-GO[®] APOMORPHINE HYDROCHLORIDE. ABBREVIATED PRESCRIBING INFORMATION. Consult Summary of Product Characteristics before prescribing. **Uses:** The treatment of disabling motor fluctuations ("on-off" phenomena) in patients with Parkinson's disease which persist despite individually titrated treatment with levodopa (with a peripheral decarboxylase inhibitor) and/or other dopamine agonists. **Dosage and Administration:** Apomorphine hydrochloride is administered subcutaneously either as an intermittent bolus injection or by continuous subcutaneous infusion. Its rapid onset (5-10 mins) and duration of action (about 1 hour) may prevent an "off" episode which is refractory to other treatments. Hospital admission under appropriate specialist supervision is necessary during patient selection and when establishing a patient's therapeutic regime. Please refer to the Summary of Product Characteristics for full details before initiating therapy. Treatment with domperidone (typical dosage 20mg three times a day) before and during apomorphine HCl therapy is essential. The optimal dosage of apomorphine HCl has to be determined on an individual patient basis; individual bolus injections should not exceed 10mg and the total daily dose should not exceed 100mg. **Contraindications:** Children and adolescents (up to 18 years of age). Known sensitivity to apomorphine or any other ingredients of the product. Respiratory depression, dementia, psychotic disease or hepatic insufficiency. Intermittent apomorphine HCl treatment is not suitable for patients who have an "on" response to levodopa which is marred by severe dyskinesia or dystonia. **Pregnancy and lactation:** Apomorphine should not be used in pregnancy unless clearly necessary. 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. It is recommended to avoid the administration of apomorphine with other drugs known to prolong the QT interval. **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. Since apomorphine, especially at high doses, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia. Apomorphine has been associated with local subcutaneous effects that can be reduced by rotation of injection sites or use of ultrasound on areas of nodularity and induration. **Side Effects:** Local induration and nodules (usually asymptomatic) often develop

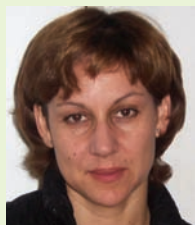
at subcutaneous site of injection leading to areas of erythema, tenderness, induration and panniculitis. Irritation, itching, bruising and pain may also occur. Rarely injection site necrosis and ulceration have been reported. Pruritus may occur at the site of injection. Drug-induced dyskinesias during "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. Dizziness and lightheadness have also been reported. Nausea and vomiting may occur, particularly when APO-go treatment is initiated, usually as a result of the omission of domperidone. Neuropsychiatric disturbances (including transient mild confusion and visual hallucinations) have occurred during apomorphine therapy and neuropsychiatric disturbances may be exacerbated by apomorphine. Positive Coombs' tests and haemolytic anaemia and thrombocytopenia 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. Yawning and breathing difficulties have been reported as has peripheral oedema. *Prescribers should consult the Summary of Product Characteristics in relation to other side effects.* **Presentation and Basic NHS Cost:** Apo-go ampoules contain apomorphine hydrochloride 10mg/ml, as follows: 20mg in 2ml – basic NHS cost £37.96 per carton of 5 ampoules. 50mg in 5ml – basic NHS cost £73.11 per carton of 5 ampoules. APO-go pens (disposable multiple dosage injector system) contain apomorphine hydrochloride 10mg/ml, as follows: 30mg in 3ml – basic NHS cost £123.91 per carton of 5 pens. APO-go Pre-filled syringes contain apomorphine hydrochloride 5mg/ml, as follows: 50mg in 10ml – basic NHS cost £73.11 per carton of 5 syringes. **Marketing Authorisation Numbers:** APO-go Ampoules: PL 06831/0245; APO-go Pens: PL 06831/0246; APO-go Pre filled syringes: PL 06831/0247. **Legal Category:** POM. **Date of last revision:** February 2010. For further information please contact: Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN, UK.

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Cognitive and Behavioural Complications of Parkinson's Disease



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The most commonly reported neuropsychiatric complications in Parkinson's disease (PD) are symptoms of depression, anxiety, and psychosis. However, some of the most interesting advances recently have been in the areas of cognitive impairment and behavioural disturbances in the form of disorders of reward and motivation, such as apathy and impulse control disorders (ICDs). These cognitive and behavioural complications, which may interlink with each other, will be the focus of this article.

Cognitive impairment in PD

Cognitive impairment, particularly in the form of executive dysfunction is common and may manifest at the same time as the onset of the motor symptoms. More extensive cognitive manifestations such as dementia in PD (PDD) may also appear and since people are living with the disease longer, the prevalence of PDD is increasing. Furthermore, a relatively new area of inquiry in cognition in PD is gaining increasing attention, namely, changes in emotionally-dependent decision-making, which may be driven by changes in limbic-based neural pathways.

Executive dysfunction or mild cognitive impairment in PD

Even in the early stages of PD, impairments in various cognitive domains may be evident in a significant minority. In one study, 42% of an incident cohort of PD sufferers had cognitive impairment on presentation.¹ In particular, executive functions (abstract reasoning, planning, working memory, attention, and temporal sequencing), recall, language, memory, and visuo-perceptual ability may be affected. In general, these deficits may initially only be evident on detailed neuropsychological testing, however, in some they may become more severe or widespread and begin to impact on non-routine daily activities. At this point, the deficits may be considered as a "mild cognitive impairment" (MCI) syndrome, although there is debate about the utility of using such a label.² MCI may be a precursor to a more severe cognitive syndrome that meets criteria for dementia (PDD), however, it is more likely that the neurotransmitter deficits underlying these mild cognitive deficits are due to

disruptions in dopaminergic pathways, whereas the deficits underlying a more obvious dementia syndrome are cholinergic.³

Dementia in PD

It is now accepted that if someone lives with PD long enough, they are likely to develop dementia. The Sydney Multicentre Study, which followed-up a cohort of 136 PD sufferers over several years, found that 83% of the 20-year survivors had developed dementia, together with a constellation of other symptoms of advanced PD including excessive daytime sleepiness (EDS), falls, freezing and hallucinations.⁴ Based on this study, the mean age at diagnosis of dementia was about 70 years old and the mean time to onset after diagnosis of PD was about 11 years. Clinically, PDD is characterised by an insidious onset and slowly progressive global cognitive decline, usually accompanied by a variety of behavioural symptoms such as apathy, hallucinations, depression, anxiety, and EDS. PDD differs clinically from dementia with Lewy Bodies (DLB) in that the dementia syndrome in PDD does not generally predate or occur at the same time as the onset of motor impairments, and perceptual abnormalities such as visual hallucinations are usually more common in DLB. Several factors may predict the conversion from PD to PDD, suggesting the presence of a "dementia-prone" subtype of PD. For example, impaired verbal fluency and visuo-perceptual functioning at diagnosis, older age at disease onset, akinetic-rigid type of PD, depression or psychosis early on in the course of the illness, orthostatic hypotension, and weight loss may all be predictors of later conversion to PDD.^{5,6} The underlying pathology of PDD is heterogeneous and may reflect Alzheimer's disease-like changes with amyloid plaques and neurofibrillary tangles, the presence of cortical Lewy bodies, as well as vascular changes.⁴ The extent of cholinergic deficit appears to correlate with the degree of cognitive impairment,⁷ and this may relate to subcortical loss of cholinergic neurones and the associated loss of ascending cortical projections, rather than intrinsic cortical neuronal loss. This cholinergic deficit is the basis for the use of cholinesterase inhibitor therapy for the pharmacological management of PDD.^{8,9} The use of the

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uncompetitive antagonist of N-methyl-D-aspartate (NMDA), memantine, may also have a role in managing PDD symptoms^{10,11}.

Decision-making abnormalities in PD

Emotionally-dependent decision-making is of increasing interest in PD due to recent studies which have shown deficits in such decision-making in people with PD. Moreover, with the relatively recent focus on ICDs in PD, this type of decision-making may be of importance as a potential basis for the development of the impulsive behaviours in the setting of dopamine replacement therapy (DRT). Broadly, such aspects of cognitive functioning have been labelled as “hot” decision-making, mediated by limbic areas (including aspects of self-control and impulsive decision-making) such as the ventral medial prefrontal cortex (VMPC) and orbitofrontal cortex (OFC), as opposed to the more “cool” or rationally-based aspects of executive function, mediated by the dorso-lateral prefrontal cortex (DLFC), all areas which may be affected by PD-related pathology. This may result in a reduced ability to interpret negative consequences or negative feedback, or take past experience into account when making decisions. Dopamine replacement therapy (DRT) may further impact on this type of cognitive functioning and it has been shown that when “on” DRT, those with PD were unable to learn to avoid undesirable or negative choices, as well as over-interpreting positive outcomes, compared to being “off” DRT.¹²

Behavioural disturbances in PD

Behavioural disturbances in PD may manifest as either apathy, or loss of motivation and drive, or the ICDs. These disorders may co-occur with depression and anxiety and other neuropsychiatric symptoms and variable degrees of cognitive change.

Apathy in PD

Apathy in neurodegenerative conditions can be defined as “a lack of interest, emotion and motivation”¹³ and is one of the most common neuropsychiatric complications in PD, occurring in over 40% of sufferers.¹⁴ Clinical correlates of apathy also include high rates of depression. Cognitive correlates include more impaired executive dysfunction, particularly working memory and verbal fluency, as well as more impaired global cognitive functioning.¹⁴ The pathophysiology of PD that might lead to apathy is linked to impairments in pathways that underlie pleasure and reward seeking.¹⁵ This is supported by studies in PD which have demonstrated blunted anticipatory responses to motivationally significant events or rewards,¹⁶ as well as striatal hypoactivation at the prospect of reward.¹⁷

Impulse control disorders in PD

“Impulse control disorders” (ICDs) in PD is a loosely defined group of behavioural conditions in PD, which was first described in the 1980s when case descriptions of an addiction to DRT were published. Later, in 2003, Driver-Dunckley described nine cases in a retrospective review of 1884 PD sufferers who developed pathological gambling (PG) following exposure to dopamine agonists (DAs).¹⁸ Since then, DRT has been considered to play a key, if not causal, role for the development of PG and possible other ICDs. Now, in the UK, all DAs have warnings about the risk of developing PG and other ICDs listed in their Summary of Product Characteristics. ICDs may

CASE REPORT

Mark Robson, 54, Lives in Royton, near Oldham, Manchester.

Mark was working as an engineer when he first noticed a slight tremor and cramping in his right hand when he was trying to write, and his handwriting seemed to be getting smaller. He was diagnosed with Parkinson's in 1998, and put on Pergolide in the November of that year. Mark tried to keep positive, taking up Chi-gung and yoga, and trained as a qualified healer. Mark at this time was married happily to his third wife.

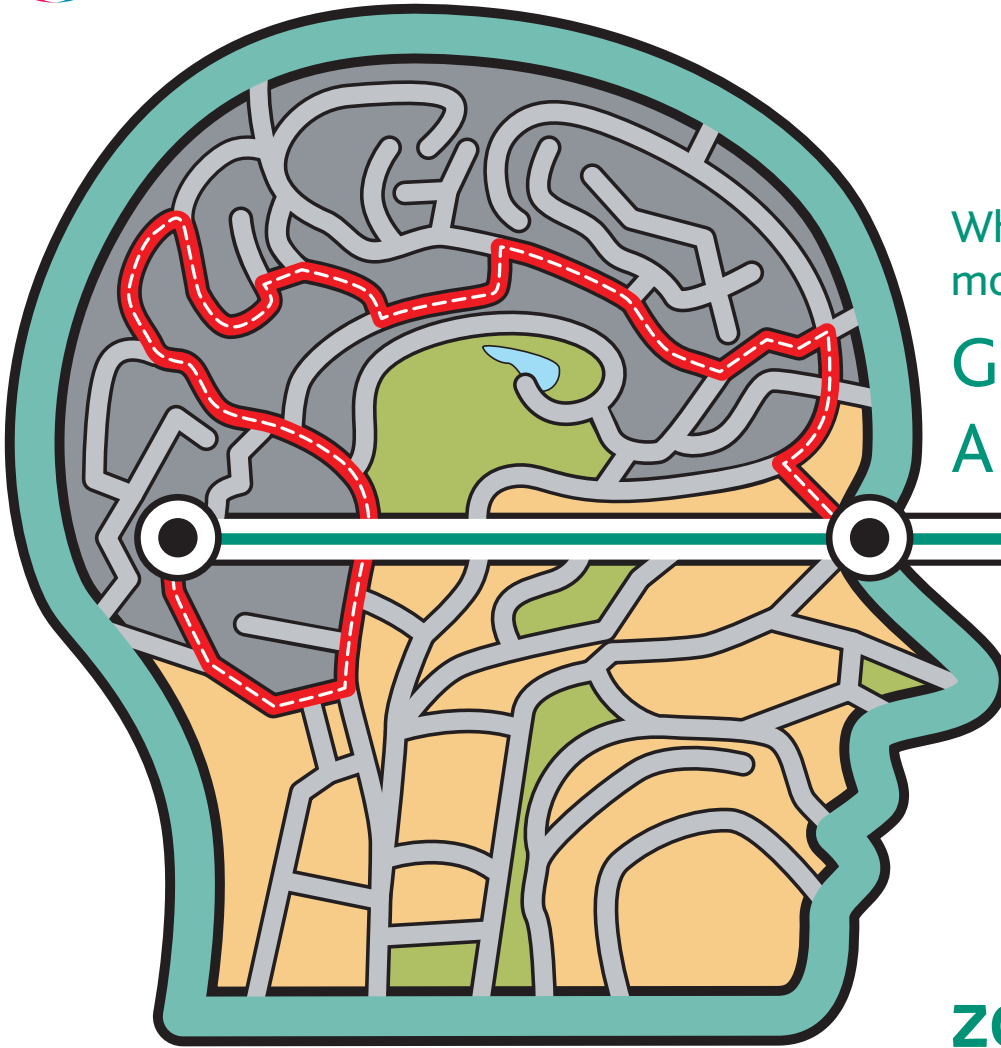
When the dosage of Pergolide was increased to combat worsening symptoms, Mark's personality began to change. In June 2004 the nightmare began. Mark became reclusive and less outgoing. His wife noticed things were different. Mark started to overeat and had no control over the amount of food he was eating. He started gambling, which was totally out of character. At first, it was interactive TV games, then internet casino sites. Mark had five credit cards, and two personal loans. He was juggling money on these, plus taking out extra loans. He estimates he was spending at least 22 hours a day on line gambling. This went on for 18 months.

He lost at least £200,000, remortgaging his house to finance his habit. Up to this point Mark had managed to keep the financial situation away from his wife. He became increasingly sneaky and conniving, and used to lie to get money to gamble – spending the mortgage money, and stealing from his wife's business – about £20,000 from her account (she was eventually declared bankrupt in October 2005). His marriage broke up.

During this time Mark was seeing his specialist at Oldham hospital – but as he wasn't aware of a possible link with medication he didn't mention the gambling addiction. It wasn't until a friend sent him an article in The Daily Mail about somebody else with Parkinson's who had a gambling habit and was blaming his medication, that the penny finally dropped. Mark re-contacted his Parkinson's specialist and was told him to come in straight away for a consultation. Then the link with Pergolide and compulsive behaviours was discussed. Mark was taken off Pergolide gradually over about four weeks. The urge to gamble disappeared.

Mark was left feeling exhausted, suicidal, and unable to cope. He was admitted to a psychiatric ward where he stayed for seven weeks. In 2006 he got divorced. As his wife had the marital home Mark went to live with his father in Fleetwood. Mark struggled to get his life back together. He was on anti-depressants, and lost about three stone. After not having had any contact with his ex-wife for four years, last year Mark and his former wife got back in touch, as Mark had hired a solicitor to prepare a case against the drug manufacturers and needed her support. They decided that they should make another go of their relationship, and remarried in November 2009. “It was a victory for us as a couple. We had been through hell and back because of a tablet no bigger than 2mm in size”. Mark has not been able to work since 2000. He is taking part in Parkinson's funded research with Dr Iracema Leroi.

Mark Robson was part of the research project funded by Parkinson's UK



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Dose and administration: Adult: Must be added to existing therapy. Initial daily dose is 50 mg in two divided doses. After one week, increase to 100 mg daily. Then increase at one weekly intervals in 100 mg increments. Can be taken once or twice daily after titration. In renal or hepatic impairment and patients not receiving CYP3A4-inducing agents consider two weekly intervals. 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 the risks. Specialist advice should be given to women who are likely to become pregnant. Women of childbearing potential must use contraception during treatment and for one month after discontinuation. **Lactation:** Excreted into breast milk. A decision must be made to either discontinue Zonegran or stop breast-feeding. **Warnings and Precautions:** Serious rashes occur in association with Zonegran therapy, including cases of Stevens-Johnson syndrome. Zonegran contains a sulphonamide group which are associated with serious immune based adverse reactions. Closely supervise and consider discontinuation in patients with unexplained rash. Cases of agranulocytosis, thrombocytopenia, leukopenia, aplastic anaemia, pancytopenia and leucocytosis have been reported. Monitor for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Use with caution in patients with risk factors for nephrolithiasis, including

prior stone formation, a family history of nephrolithiasis and hypercalcaemia. Evaluate and monitor serum bicarbonate levels in patients who have: underlying conditions which might increase the risk of metabolic acidosis; increased risk of adverse consequences of metabolic acidosis; symptoms suggestive of metabolic acidosis. If metabolic acidosis develops and persists, consider reducing the dose, discontinuing or alkali treatment. 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, consider discontinuation. In cases of severe muscle pain/weakness with or without fever, assess markers of muscle damage and consider discontinuation. Zonegran 100 mg capsules contain E110. Caution in patients less than 40 kg. In patients with weight loss consider dietary supplement, increased food intake or discontinuation. **Drug Interactions:** No clinically relevant pharmacokinetic effects on carbamazepine, lamotrigine, phenytoin, sodium valproate, oral contraceptives (ethinylestradiol or norethisterone). Insufficient data with carbonic anhydrase inhibitors, e.g. topiramate. Zonegran was not affected by lamotrigine or CYP3A4 inhibitors. Caution with drugs which are P-gp substrates. Avoid concomitant administration with drugs causing urolithiasis. Zonisamide is metabolised partly by CYP3A4, N-acetyl-transferases and conjugation with glucuronic acid; therefore caution with substances that can induce or inhibit these enzymes. **Side effects:** The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia. Adverse reactions associated with Zonegran in clinical studies and post-marketing surveillance: Very common effects ($\geq 1/10$): anorexia, agitation, irritability, confusional state, depression, ataxia, dizziness, memory impairment, somnolence,

diplopia, decreased bicarbonate. Common effects ($\geq 1/100$, $< 1/10$): ecchymosis, hypersensitivity, affect lability, anxiety, insomnia, psychotic disorder, bradyphrenia, disturbance in attention, nystagmus, paraesthesia, speech disorder, tremor, abdominal pain, constipation, diarrhoea, dyspepsia, nausea, rash, nephrolithiasis, fatigue, influenza-like illness, pyrexia, weight decreased. Uncommon ($\geq 1/1000$, $< 1/100$): pneumonia, urinary tract infection, hypokalemia, anger, aggression, suicidal ideation, suicidal attempt, convulsion, vomiting, cholecystitis, cholelithiasis, calculus urinary. For very rare side effects see SmPC. Isolated cases of Sudden Unexplained Death in Epilepsy Patients (SUDEP). Post-marketing data suggests patients aged ≥ 65 years report a higher frequency of Stevens-Johnson syndrome and Drug Induced Hypersensitivity syndrome. **Legal Category:** POM. **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, European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN. **Date of preparation:** July 2009.

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occur in up to 14% of PD sufferers and include PG, hypersexuality, compulsive shopping and binge eating.¹⁹

Pathological gambling (PG) is one of the most commonly reported and clinically dramatic of the behavioural disturbances associated with PD. It characteristically arises after the introduction of a DA and manifests in a change in behaviour that involve seeking out opportunities to gamble, including scratch card or lottery addiction, betting, internet or casino gambling and stock market trading. Such PG behaviour is typically difficult to control by the affected individual, progresses to involve larger amounts of money and greater risks, and continues despite adverse consequences. A recent review examined reports of 177 PD sufferers who developed PG and concluded those affected are more commonly male, young and have psychiatric co-morbidity and use DAs.²⁰

Hypersexuality (HS) in PD, which also usually occurs with a change in DRT, may appear in isolation, or in association with other ICDs. It may take the form of an enhanced libido, greater frequency of male erections, new sexual orientations, practices and even fetishes and may be accompanied by changes in mental state such as hypomania or disinhibited behaviour.

Finally, dopamine addiction, also known as "dopamine dysregulation syndrome" (DDS) involves a progressive dependence on DRT, accompanied by marked dyskinesia, demands for more DRT despite being "on" motorically,

hoarding behaviours associated with wanting more DRT, a reluctance to cut back on the medication, and marked irritability and withdrawal symptoms when denied access to DRT. DDS is often accompanied by purposeless, repetitive and stereotyped behaviours ("punding"), other ICDs and mood changes, and may be more closely linked to the use of levo-dopa than DAs. There is debate about whether DDS is a separate phenomenon from the ICDs since it is more closely related to excessive dopaminergic doses compared to the ICDs.

Are cognitive changes and behaviours linked in PD?

Since both apathy and the ICDs appear to involve reward and decision-making pathways, the question of whether they may overlap and how they may be linked to cognitive changes arises. Our own data suggest that rates of attentional impulsivity may be higher in those with PD-related apathy compared to PD-controls, and that ICD sufferers in PD have higher rates of apathy compared to PD-controls.²¹ In apathy in PD, the predominant cognitive dysfunction involves executive dysfunction, particularly in set-shifting and verbal fluency,¹⁴ supporting the notion that cognitive deficits might be driving behaviours. In the ICDs, on the other hand, executive function may often be intact but here the key "cognitive lesion" may be disruption to emotionally-based decision-making, leading to a pattern of "cognitive impulsivity" that may in part drive

impulsive behaviours in the context of DRT.^{22,23}

While the field of ICD studies in PD is relatively young, a few studies of an experimental nature have started to emerge and involve examining PD study participants both "on" and "off" medication while doing specific cognitive tasks. The key overall finding from these studies is that neural reward pathways, including the ventral striatum (VS), appear to be implicated in ICD pathophysiology and this may be impacted upon by DRT, and that dopamine is more readily released from the VS during reward-related tasks.²⁴ With this model, DRT may precipitate the development of impulsivity due to modulation of reward sensitivity by altering the "hot"-limbic/"cool"-executive system balance in favour of the "hot"-limbic loop.²⁵ This, in turn, leads to goal directed, impulsive behaviour, which may become addictive, and, once again, cognition appears to drive behaviour.

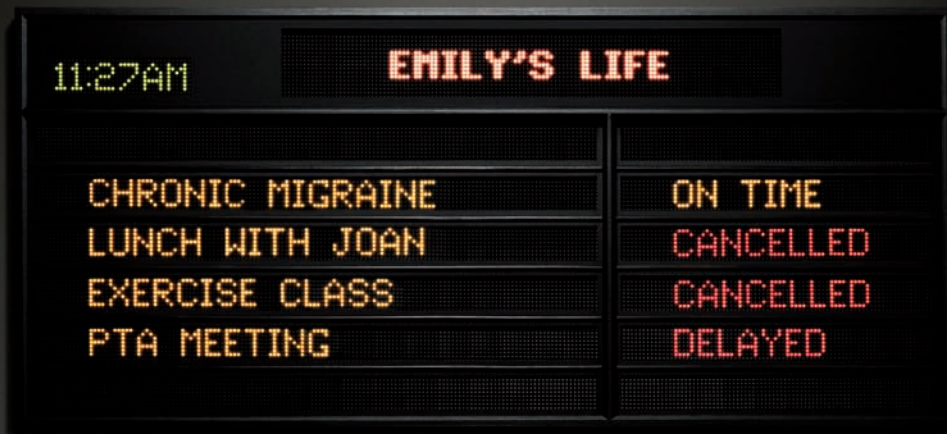
Conclusion

The changes in various levels of cognitive functioning in PD, as described above, and the putative links to behavioural changes, result in a challenging clinical scenario. In examining either behaviour or cognition in neurodegenerative conditions such as PD, it is important to consider how they may be interlinked and how their combined effect may manifest in the PD sufferer. ♦

Dr Leroi has just finished a three year research project in this area funded by Parkinson's UK.

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in some cases). Other adverse events reported include dysarthria, abdominal pain, vision blurred, pyrexia, focal facial paralysis, hypoaesthesia, malaise, myalgia, pruritis, hyperhidrosis, diarrhoea, anorexia, hypoaacusis, tinnitus, radiculopathy, syncope, myasthenia gravis, erythema multiforme, dermatitis psoriasisiform, vomiting and brachial plexopathy. Also, rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Rare reports of serious and/or immediate hypersensitivity (including anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea) associated with BOTOX[®] use alone or in conjunction with other agents known to cause similar reaction. Very rare reports of angle closure glaucoma following treatment for blepharospasm. New onset or recurrent seizure occurred rarely in predisposed patients, however relationship to botulinum toxin has not been established. Needle related pain and/or anxiety may result in vasovagal response. **Basic NHS Price:** 50 Units: £77.50, 100 Units: £138.20, 200 Units: £276.40. **Marketing Authorisation Number:** 50 Units: 426/0118, 100 Units: 426/0074, 200 Units: 426/0119. **Marketing Authorisation Holder:** Allergan Ltd, Marlow International, The Parkway, Marlow, Bucks, SL7 1YL, UK. **Legal Category:** POM. **Date of preparation:** July 2010. Further information is available from: Allergan Limited, Marlow International, The Parkway, Marlow, Bucks SL7 1YL.

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Neurological literature: Headache (Part 7): Megrim

A Google search for megrim will reveal several definitions, including a species of left-eyed flatfish (the whiff, or *Lepidorhombus whiffiagonis*), although neurologists will recall that this word is also an archaic (some would say obsolete) word for migraine. (Pubmed contains no references to megrim, as far as I can ascertain.) Other usages of megrim are reported to include:

- a caprice, fancy, whim or fad (often in the plural, megrims); and
- depression, melancholy, low spirits or unhappiness.

An example of the latter usage is said to be from Samuel Richardson's *History of Sir Charles Grandison* (1753) wherein Lady G writes to Miss Byron (volume VI, letter xlv) "If these megrims are the effect of Love, thank Heaven, I never knew what it was".¹ It remains possible, however, that this could equally well refer to headaches. *Sir Charles Grandison* was the favourite novel of Jane Austen (1775-1817), large passages of which she knew by heart, and it may have been one stimulus, specifically imitation, for her use of headache as a plot device in several of her novels, as well as in other written work.²

Lane & Davies explain that Galen's term "hemigrania" was translated into low Latin as "hemigranea", and that through successive transliterations and abbreviations this evolved by the 16th century into megrim in English, denoting sick headache, blind headache and bilious headache³ (the latter term was still in common usage in the twentieth century, used for example by my maternal grandmother⁴). The Oxford English Dictionary has its earliest references to megrim in the sense of headache dating to the mid-fifteenth century, hence postdating the earliest recorded use of headache (ca. 1000AD) by more than four centuries.⁵ A seventeenth century translation of the *Chirurgical Works* of the French surgeon Ambroise Paré (1510-1590) includes the statement:

The Megrim is properly a disease affecting the one side of the head, right or left.

Perhaps most famously in the neurological context, the word megrim was used by Edward Liveing in the title of his 1873 work, one of the seminal works in the history of headache, *On Megrim, Sick-Headache, And Some Allied Disorders: A Contribution To The Pathology Of Nerve-Storms*⁶ which addressed his ideas on the pathophysiology of these headaches.⁷ The following year Sydney Ringer wrote in the *BMJ* on the action of hydrate of croton-chloral on megrim,⁸ and later in the same decade, 1879, Edward Nettleship noted that:

It is well known that certain of the subjects of megrim are liable to a very peculiar affection of sight, in which a part of the field of vision becomes obscured by a flickering or waving cloud, the edges of which in many persons

*are sharply defined, serrated and brilliantly coloured.*⁹

Galezowski used the term "ophthalmic megrim" to describe central retinal vein occlusion associated with migraine in 1882.¹⁰

Some literary uses of megrim may also be noted here, some almost contemporaneous with its aforementioned uses in the 19th century medical literature. The word was certainly known to George Eliot, pseudonym of Marian Evans (1819-1880). In *Adam Bede* (1859), her first major novel, it is said of one female character:

...it was a pity she should take such megrims into her head, when she might ha' stayed wi' us all summer, and eaten twice as much as she wanted, and it 'ud niver ha' been missed.

In *Felix Holt, the Radical* (1866), a character asks:

Can't one work for sheer truth as hard as for megrims?

OED records this as an example of megrims in the sense of a whim, fancy or fad. Another example may be Dr Tertius Lydgate in *Middlemarch* (1871-2) who is reported to be:

...abrupt but not irritable, taking little notice of megrims in healthy people.

Eliot's contemporary Wilkie Collins (1824-1889) was also familiar with the word. For example in *Armadale* (1866), one character asks of another:

How did you manage to clear your head of those confounded megrims?

The context suggests that this may refer to either fancies or low spirits, but in *The Moonstone* (1868), possibly Collins's best known work, its use certainly suggests the possibility of headaches:

This was the first attack of the megrims that I remembered in my mistress since the time when she was a young girl.

Moving to a more contemporary literary use of the word megrim, two examples may be found in the oeuvre of Stephen King (born 1947). In *Gerald's Game* (1992) it is used in the sense of fancy, whim, freak, caprice:

No, she thought her imagination had more than earned its right to a few hallucinatory megrims, but it remained important for her to remember she'd been alone that night.

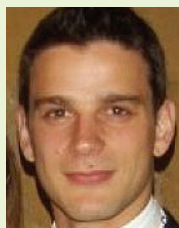
In *Desperation* (1996), it is used in the sense of low spirits, unhappiness:

He was turning around, zipping his fly, talking mostly to keep the megrims away (they had been gathering like vultures just lately, those megrims), and now he stopped doing everything at once.

One can understand how this word may perhaps appeal to King's sensibilities.

On a final, musical, note, the composer Barry Ferguson uses megrim in his song *The Ruined Maid* (1997), again in the sense of melancholy, from a cycle of songs written for Catherine King (listen at www.catherineking.org). ♦

RNA Interference and Neurological Disorders



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RNA interference (RNAi) is a powerful mode of post-transcriptional gene silencing, the discovery of which earned Fire and Mello the 2006 Nobel Prize in Physiology or Medicine. Since their seminal work published in 1998, which led to the identification of double-stranded RNAs (dsRNAs) as being responsible for RNAi in a sequence-specific manner,¹ it has become clear that RNAi is an essential and ubiquitous process in all eukaryotic cells and organisms. It is especially critical in stem cells and during development, and it is now appreciated that dysregulation of RNAi function is a central feature of pathological processes, including cancer and neurological disease. Moreover the powerful ability of RNAi to silence genes has therapeutic potential.

RNAi biology

RNAi refers to the sequence-specific silencing of messenger RNA (mRNA) transcripts directed by short, 21-23 nucleotide antisense RNA species. The genes responsible for initiating RNAi are part of an evolutionary conserved cellular pathway that processes endogenous triggers of RNAi, termed microRNAs (miRNAs), into mature sequences capable of directing the silencing of sequence-matched mRNA targets (Figure 1). Over 900 human miRNAs have now been identified within the genome, and several have been shown to silence the expression of anywhere from tens to hundreds of mRNA transcripts at a time.² Thus the natural RNAi pathway within cells represents a powerful post-transcriptional gene regulation network that helps to maintain and enhance complexity arising from transcription of the genome, whilst the dysregulation of this network can have disease-causing potential.

miRNAs and neurological disease

Given their ability to enhance the complexity of the transcriptome, it is perhaps no surprise that the central nervous system (CNS) is enriched in miRNA expression. Here they display tight spatial and temporal expression patterns, and have now been shown to have key roles in multiple aspects of neurobiology including neuronal-lineage determination, synaptogenesis and neurogenesis

among others.³ Further to this, abnormalities at almost every stage of miRNA processing have now been linked to disease, and several neurological disorders are among those now identified as linked to miRNA dysregulation. Profiling of miRNA expression in post-mortem tissue samples from patients with neurological disorders such as Alzheimer's disease (AD),⁴⁶ Huntington's disease (HD),⁷ Parkinson's disease (PD),⁸ schizophrenia,⁹ and autism¹⁰ have identified miRNAs that demonstrate either increased or reduced expression relative to control tissues (Table 1); implicating their involvement in the disease process. Similarly, a plethora of dysregulated miRNAs have also been identified in pre-clinical neurological disease models. Importantly, such patterns of miRNA dysregulation may now hold promise as novel diagnostic or therapeutic biomarkers for neurological diseases, as has already been shown for several cancers. However it is unclear at present whether alterations in the expression of miRNAs across these disorders are causative of the disease phenotypes, or merely consequences of other primary defects. This will be important to determine in future since it could reveal novel therapeutic strategies involving for example the use of miRNA inhibitors or mimics to modulate miRNA activity.

In addition, the 3'UTRs of mRNAs typically contain target seed-matched sequences for miRNAs and are known to be a common site for genetic variation. Disease-linked single nucleotide polymorphisms (SNPs) have now been reported in specific 3'UTR miRNA target sites in cases of Tourette's syndrome,¹¹ PD,¹² TDP43-positive frontal temporal dementia¹³ and even in individuals displaying aggressive behavior¹⁴ (Table 1). These SNPs can lead to either reduced miRNA silencing of the mutated transcript by the targeting miRNA, or tighter regulation by the miRNA due to strengthening of the miRNA-binding site. Conversely, SNPs in miRNA transcripts themselves have also been reported for non-CNS disorders and this could be an additional mechanism found to link miRNAs to neurological disease in future either through direct effects on the processing of the miRNA or directly on target mRNA silencing.

RNA interference is of already central biological importance and it promises to make a major clinical impact, particularly in the neurosciences

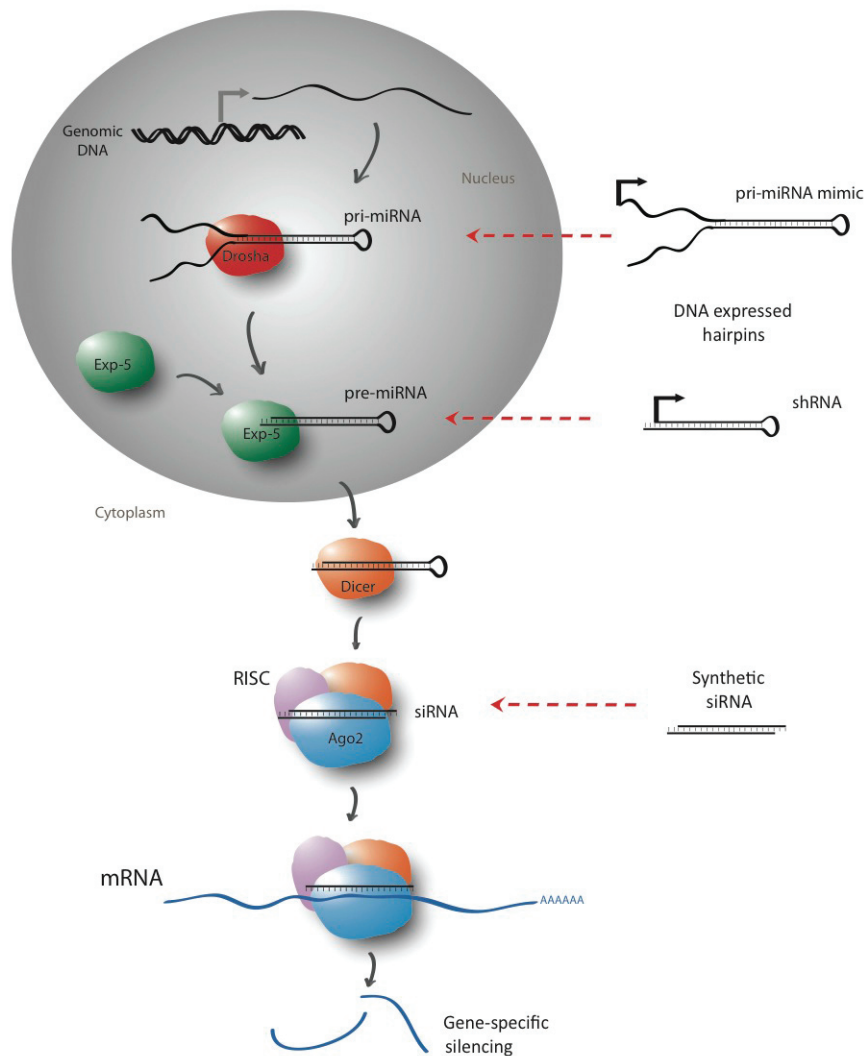


Figure 1. Mechanism and Exploitation of the RNAi pathway.

In the endogenous RNAi pathway, primary miRNA (pri-miRNA) sequences are transcribed from genomic DNA. Complementary base pairing between separated regions of the pri-miRNA sequence allows characteristic stem-loop secondary structures to form which are subsequently recognised by the ribonuclease enzyme, Drosha. The resulting cleavage within the stem produces a pre-miRNA precursor, with characteristic two nucleotide overhangs at the 3' end. These overhangs serve as a recognition signal for nuclear export by Exportin-5, and then for further processing by Dicer. Removal of the loop-region of the pre-miRNA by Dicer results in production of a dsRNA duplex, or short interfering RNA (siRNA) which initiates the formation of the Argonaute (AGO) protein-containing RNA-induced silencing complex (RISC). Within RISC a thermodynamic selection process selects one of the two siRNA strands as the active guide strand, referred to as the mature miRNA, that will be used to direct target mRNA silencing whilst the other strand is discarded. RISC subsequently scans the retained mature miRNA across mRNA sequences, and in particular the 3' untranslated regions (3'UTRs), searching for sequence homology to the mature miRNA. When identified, the AGO proteins within RISC initiate target mRNA silencing through translational repression in the case of incomplete homology, or alternatively through target mRNA degradation if homology to the mature miRNA sequence is complete. Gene silencing based therapy can exploit several points of the endogenous RNAi pathway, including expressed triggers of RNAi such as pri-miRNAs and shRNAs, as well as siRNA forms.

Manipulation of RNAi pathway for neurological disease therapy

Therapeutic exploitation of the RNAi mechanism described above is also a prominent focus of research. For several neurological diseases it is likely that silencing genes that are over-expressed or which harbour pathogenic mutations would be therapeutically beneficial, especially where mutations result in gain-of-function. Silencing of pathogenic human transgenes in mice leads to phenotypic improvements in both HD¹⁵ and spinocerebellar ataxia 1 (SCA1)¹⁶ mouse models. In the HD models, RNAi treatment that reduces

mutant human and wild-type mouse Huntington mRNA transcripts concomitantly by ~60% has been shown to lead to improved motor coordination over sham-treated littermates, and importantly to an increase in life expectancy.¹⁵ Similarly, cerebellar degeneration was reduced and an ataxic behavioural phenotype improved following RNAi treatment leading to reduced ataxin-1 in the SCA1 mice.¹⁶ However, the non-allele specific silencing used in these studies would only be applicable to those diseases in which the function of the normal wild-type gene is non-essential. For several neurological diseases, a func-

tioning copy may be important, if not a necessity. In these cases, allele-specific silencing of the mutant gene only would be desirable. Though extensive screening is required to identify RNAi triggers capable of discriminating between wild-type and mutant transcripts, allele-specific therapies have been demonstrated in neurological disease models of SCA3, frontotemporal dementia, SCA7 and HD.^{17,19}

The choice of RNAi trigger is also of importance. Gene-specific silencing can be achieved using any of the processed small RNA species produced in the natural RNAi pathway as a method to target a gene of interest (Figure 1). Whilst pri-miRNA mimics and shRNAs can be expressed from DNA-encoded plasmids to allow incorporation into viruses for long-lasting expression, chemically synthesised siRNAs are delivered as dsRNA duplexes that are targets for nuclease digestion and rapid clearance from the body, making their effects short-lived. However one concern that must be addressed before routine use of RNAi in the clinic is that all three approaches can direct off-target silencing of mRNA transcripts with near-complete base-pairing to the antisense species. Thus, delivery of the RNAi trigger should ideally be restricted to only the cell-type of interest where possible to limit this undesirable silencing.

The transient nature of a siRNA-based therapy lends itself to one-off treatments for infectious or relapsing diseases. For example, intracranial injections of siRNAs targeting the Japanese encephalitis virus or Nile river virus have prevented a lethal phenotype in viral challenged mice.²⁰ In contrast, one-off treatments using an shRNA or pri-miRNA mimic expressed from within a suitable viral vector could lead to long-term gene silencing more suitable for chronic neurological diseases such as PD and HD.¹⁵ However these DNA-encoded RNAi triggers should ideally be modified to allow inducible or even neuronal-specific expression as these characteristics would be particularly useful to limit off-target silencing of near complete base-paired transcripts to the RNAi trigger.

Finally, one of the biggest challenges in developing RNAi-based therapies for neurological disorders is that of delivery to the CNS. The most common viral approaches for RNAi delivery in pre-clinical models are intracranial injections of integrating lentiviruses or non-integrating adeno-associated viruses (AAVs). However, it is unclear whether this will become a preferred method of administering treatment in patients due to the invasive nature of administration. Clearly, identification of novel methods of traversing the blood-brain barrier (BBB) following systemic injection are required. Encouragingly, transvascular delivery of a siRNA complexed with a neuronal targeting-peptide across the BBB to the striatum, thalamus and cortex has been demonstrated *in vivo*.²⁰ Likewise, the use of



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ART-EU2181



EBTARP-10-193

Preparation date: May 2010

Table 1. Neurological disorders with reported miRNA abnormalities

Disease	miRNA abnormality	Functional effect	Ref.
Alzheimer's Disease	Decreased expression of miR-29a/b-1 cluster	miR-29a and miR-29b-1 regulate BACE-1 expression. Loss leads to abnormally high BACE-1 levels	4
Alzheimer's Disease	Decreased expression of miR-107	miR-107 regulates BACE-1 expression. Loss leads to abnormally high BACE-1 levels. Loss seen in early stages of disease	6
Alzheimer's Disease	Decreased expression of miR-106b	miR-106b regulates APP expression	5
Huntington's Disease	Decreased expression of miR-9/9*	miR-9/9* is a bidirectional miRNA with one strand, miR-9, regulating the transcriptional regulator REST, and the other strand, miR-9*, regulating CoREST. In turn REST and CoREST negatively regulate miR-9/9* such that double negative feedback loop is seen	7
Parkinson's Disease	Decreased expression of miR-133b	miR-133b regulates maturation and activity of midbrain dopaminergic neurons in subsequent murine models through a negative feedback loop with transcription factor Pitx3	8
Parkinson's Disease	Polymorphism in fibroblast growth factor 20 target site of miR-433	Parkinson's disease-associated polymorphism leads to reduced miR-433 repression of target and subsequent downstream increase in α -synuclein expression	12
Schizophrenia	Decreased expression of miR-26b, miR-92, miR-24 and miR-30e	Unknown mechanisms. Upto 15 miRNAs decreased and 1 increased with microarrays. Confirmed 4 to be significant with qPCR	9
Autism	Dysregulated expression of 9 miRNAs	Unknown mechanisms. Upto 28 miRNAs dysregulated in initial analysis. Confirmed 9 to be significant with further analysis	10
Tourette's Syndrome	Polymorphism in Slit and Trk-like 1 target site of miR-189	Tourette's-associated polymorphism leads to enhanced miR-189 repression of target site	11
TDP43-frontal temporal dementia	Polymorphism in progranulin target site of miR-659	Common polymorphism leads to enhanced miR-659 repression of target and is associated with 3-fold increase in susceptibility to disease	13
Aggressive behaviour	Polymorphism in serotonin 1B receptor target site of miR-96	Common polymorphism leads to enhanced miR-96 repression of target and is associated with increased aggression	14

systemically injected, pegylated immuno-liposomes carrying shRNAs or siRNAs has impressive site-specific knockdown in induced in vivo models of intracranial brain cancer.^{21,22} A new range of nanotechnology vehicles are additionally showing promise such as gold nanorod nanoplexes incorporating siRNAs which cross an in vitro BBB model²³ and the use of self-derived exosomes that have been modified with targeting moieties in our laboratory. Finally, certain viruses such as AAV9 have been shown to cross the BBB, and it will be important to see how these may be harnessed for RNAi therapeutics in future.

Conclusion

Within the last decade our understanding of RNAi has revealed it to be of central importance in regulating genome activity. Not surprisingly for a biological process of such importance, RNAi dysfunction is now notable in many diseases, including neurological disorders. Moreover, our ability to exploit the power of RNAi silencing has moved rapidly to the point where RNAi-based therapeutics are already in clinical trials, and such approaches are well advanced in numerous pre-clinical neurological disease models. The future will inevitably reveal much more on the role of RNAi, and miRNAs in particular, in fundamental neurological processes and functions. It will also very likely see the first RNAi-based clinical trials in patients with neurodegenerative disease in the next five years. ♦

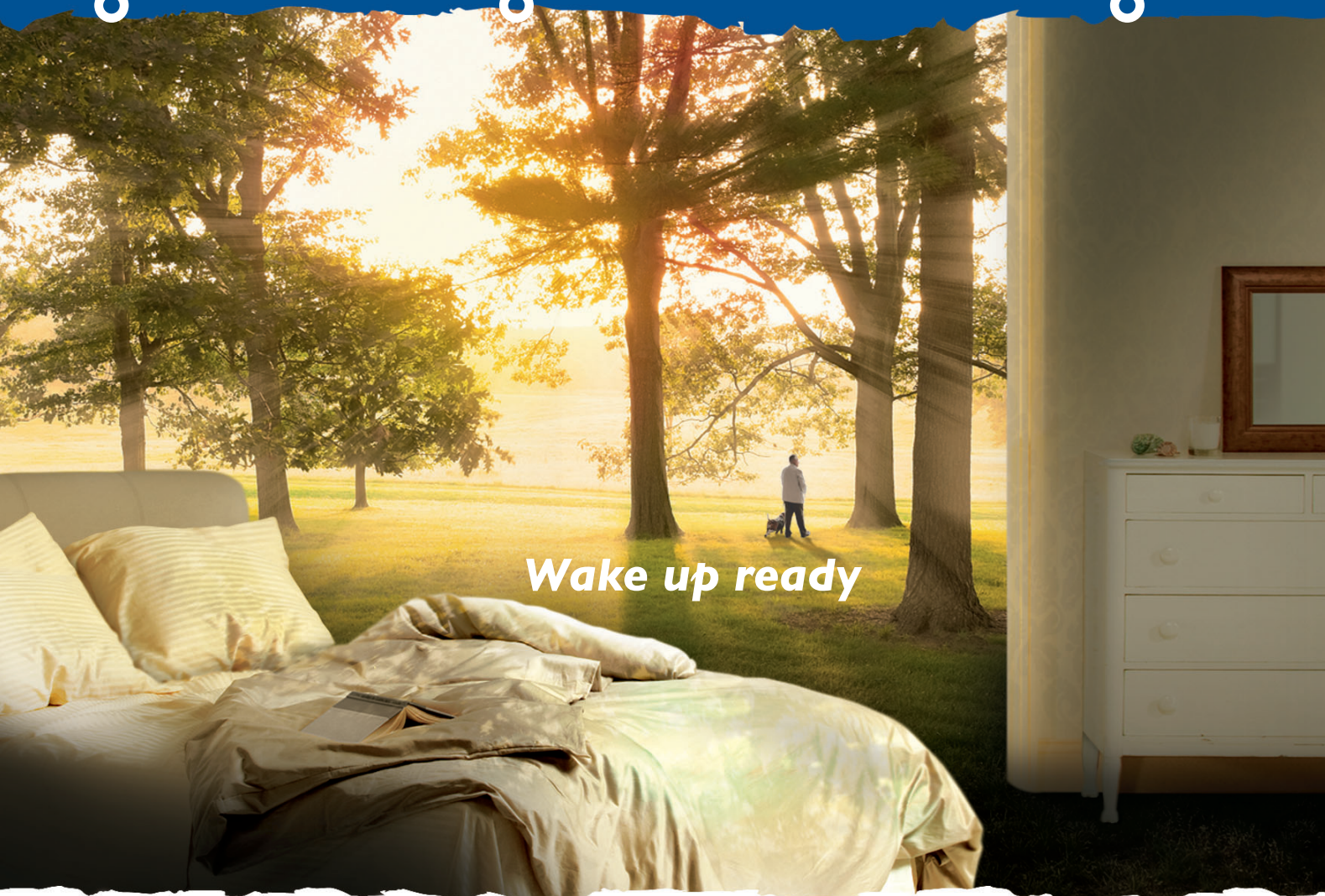
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The Persistent Mystery of the Basal Ganglia's Contribution to Motor Control



Pietro Mazzoni

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In the second article in our series on motor control, we turn our attention to the persistent mystery of what the basal ganglia actually do. We present an update on the canonical 'circuit diagram' of Alexander and colleagues, and discuss some new ideas on the role of the basal ganglia in selection of the parameters of action.

Martyn Bracewell, Series editor

The role of the basal ganglia (BG) in motor control has long been mysterious. These nuclei were always at a disadvantage, relative to other motor structures, with regards to hypotheses about their functions. Consider, for example, the primary motor cortex. It has direct projections to spinal motor neurones; electrical stimulation elicits movement; and lesions cause weakness. It was thus natural to hypothesise that the motor cortex encodes motor commands.

For the BG, on the other hand, a simple intuition is elusive. These nuclei receive information from many brain regions and project to brain structures that drive actions, suggesting a role in motor control. However, the clinical symptoms caused by BG disorders, such as rigidity, reduction of movement speed and amplitude, involuntary movements, and abnormal postures, are so varied and complex that a simple motor hypothesis is difficult to formulate.

Marsden synthesised a vast body of knowledge regarding motor abnormalities due to BG disorders, and hypothesised that the BG "are responsible for the automatic execution of learned motor tasks."¹ This hypothesis embodied the fundamental idea that the BG do not simply make movement possible, but rather that they make it possible to move in a certain manner. Indeed, early neurophysiologic studies found neural activity that was frustratingly difficult to relate to simple movement parameters, such as amplitude and direction, and was greatly affected by non-motor factors. Only years later did evidence emerge of how neural activity might encode whether a movement is executed automatically² and whether it is executed as a "learned" motor task.³

A canonical circuit for the BG

These conceptual difficulties did not dissuade researchers from a painstaking effort to establish

the anatomical, chemical, and physiological connectivity of the BG. This "bottom-up" approach identified a circuit (the motor loop; Figure 1A) connecting the BG and the motor cortical areas, which became the working model for hypotheses about BG function. In addition, this circuit was found to be one of several parallel circuits linking different parts of the basal ganglia to different cortical regions. Alexander and colleagues' review⁴ introduced two ideas that have fundamentally influenced our notions of BG function: the BG's circuitry is specifically suited to a particular type of computation (processing signals from multiple brain structures to influence behaviour), and this computation is carried out over multiple functional domains (motor, oculomotor, cognitive, and emotional).

The motor circuit is a loop in which motor and other cortical areas project to the BG, which in turn project back to motor cortical areas by way of the thalamus. In early formulations of this loop⁵ (Figure 1A), the striatum is the sole input nucleus, receiving information from motor cortical areas. The striatum projects to the internal segment of the globus pallidum (GPi) by the "direct pathway". GPi is the output nucleus, projecting to thalamus, and thence to motor cortical areas. The remaining nuclei (external segment of the globus pallidum, GPe, and subthalamic nucleus, STN) are part of the BG's internal circuitry, forming the "indirect pathway." The substantia nigra pars compacta (SNc) has a modulatory role, via its dopaminergic projection to the striatum.

Major features of this circuit are that the striatum inhibits GPi (via the direct pathway), and GPi, in turn, inhibits motor cortical areas. These features suggested that the BG tonically inhibit movement, and that when a movement is to occur, an excitatory signal from motor cortical areas causes the striatum to briefly inhibit GPi.



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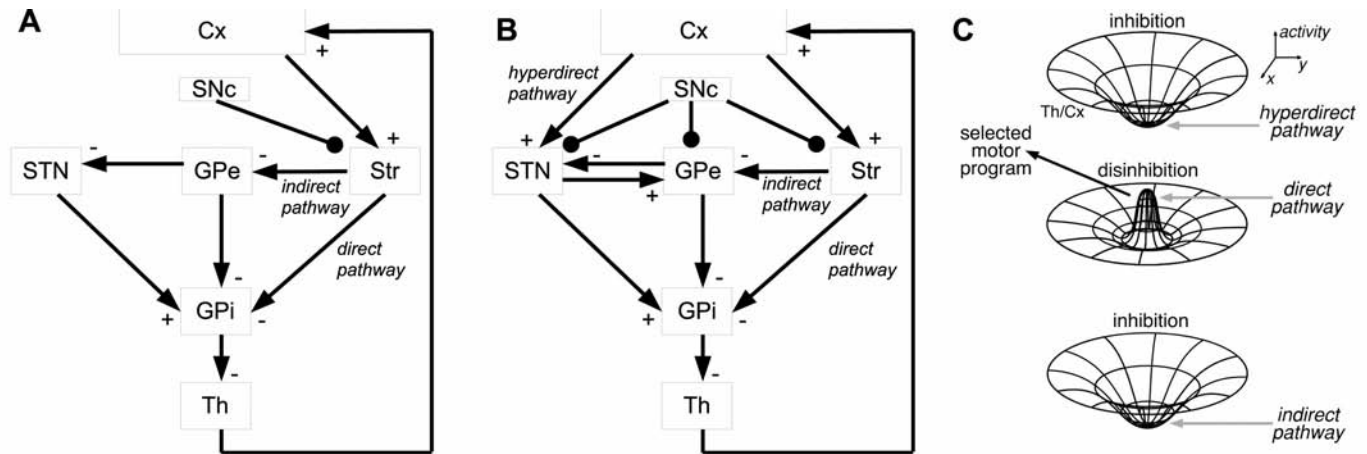
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Figure 1: Schematic diagram of the motor cortico-BG loop.



A. Early version of the model circuit.⁵ The striatum receives cortical signals related to a desired movement, and projects to thalamus, which in turn projects to motor cortical areas. Projections to brainstem structures are not shown. Excitatory (glutamatergic) synapses are indicated as arrows with "+", inhibitory (GABAergic) synapses as arrows with "-". Dopaminergic synapses (from the SNc) are indicated as filled circles. Cx, cortex; GPe, external segment of globus pallidum; GPi, internal segment of globus pallidum; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; Str, striatum; Th, thalamus.

B. Updated version of the cortico-BG loop. In addition to the connections shown in (A), there is an excitatory connection from cortex to STN (hyperdirect pathway) and an excitatory connection from STN to GPe.

C. Dynamic model of basal ganglia function explaining activity changes in thalamus and/or cortex (Th/Cx) caused by sequential inputs through the hyperdirect (top), direct (middle), and indirect (bottom) pathways. Time (t) proceeds from top to bottom. (Adapted, from Nambu et al.,⁹ with permission from Elsevier).

Thus inhibition of motor cortex is temporarily removed (disinhibition) and the desired action can occur. The indirect pathway (striatum to GPe to STN to GPi) balances the inhibitory effect of the direct pathway. Dopamine from SNc to striatum plays a modulatory role by setting the excitability of direct and indirect pathways.

Dysregulation of this circuit successfully explains certain motor abnormalities in Parkinson's disease (PD) and other motor disorders.^{5,6} In PD, for example, dopamine depletion in the SNc results in reduced activation of the direct pathway. This pathway is therefore less effective in overcoming the GPi's tonic inhibition of motor cortex, and movements thus become more difficult to initiate. In Huntington's disease, degeneration of neurons in the indirect pathway leads to a reduction of the GPi's tonic inhibition of motor cortex, and thus to the occurrence of involuntary movements. These descriptions became the basis for novel, circuit-based symptomatic treatments for PD and other movement disorders, namely, focal lesions and deep-brain stimulation of the BG.⁷

The discovery of the cortico-BG loop set the stage for a further major conceptual advance. Mink and Thach proposed that the BG "filter" motor plans, so that neural signals for desired movements are enhanced and those for similar but undesired movements are suppressed.⁸ They posited a "centre-surround" organisation of projections from striatum to GPi, which refines a cortical motor command so that the desired movement is enabled and other competing motor programs are inhibited.

A "hyperdirect" pathway

In the last two decades, there have been several advances in our understanding of anatomy and physiology of this "canonical" BG circuitry. In this updated description,^{9,10} the STN joins the striatum as an input nucleus receiving cortical projections (Figure 1B). The STN is now considered part of a "hyperdirect" pathway that contributes to the filtering action of direct and indirect pathways, helping to facilitate desired movements and inhibit competing motor programs. Recordings from these structures suggest a temporal evolution of this process.⁹ The first event associated with a cortical motor signal is activation of the STN via the "hyperdirect" pathway (cortex-STN-GPi), which causes global excitation of GPi and momentary suppression of all movements. Activation of the direct pathway (cortex-striatum-GPi), a few milliseconds later, inhibits only GPi neurons encoding the desired movement, and thus activates the desired motor program through disinhibition of selected thalamic targets. Finally, a signal through the indirect pathway (cortex-striatum-GPe-STN-GPi) puts an end to the motor command and terminates the movement.

This updated model of the motor circuit introduced temporal dynamics to signal processing in the BG. The pathophysiology of akinesia in a primate model of PD can now be described in temporal and spatial terms: when a movement is triggered by the cortex, abnormally large signals through hyperdirect and indirect pathways suppress larger-than-normal areas of thalamus/cortex, and signals through the direct pathway are reduced in amplitude

and duration. Smaller areas of the thalamus/cortex are thus disinhibited for a shorter period of time than normal, and the desired motor program cannot be released.¹¹

Action selection and reinforcement learning

Our current understanding of BG circuits offers a substrate on which to map hypotheses about action selection, reward-driven behaviour, and reinforcement learning. Theoretical and behavioural studies of learning had long predicted the existence of mechanisms for selecting an optimal action among several choices, and for learning to do so based on reward and penalty. The convergence of cortical signals onto the BG, and the adaptive temporal relationship of striatal dopamine signals to reward prediction, are ideal candidates for implementing reinforcement learning algorithms.^{12,13} At the synaptic level, dopaminergic projections from SNc to striatum and STN have the power to adjust the strength of cortical projections to these nuclei, allowing the possibility of precisely fine-tuning the effect of BG processing of cortical signals.¹⁴ These mechanisms for synaptic adjustments are well suited to the modification of action selection mechanisms based on reinforcement learning, and thus to the development of automatic, habit-based behavioural patterns.³

Can such computations help explain clinical movement abnormalities? Certain deficits, such as increased delays in movement onset in PD and abnormal postures of dystonia, can be related, respectively, to inadequate flow of signals through the direct pathway and to



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abnormal balance between GPI excitation and inhibition.^{5,8} It is not obvious, on the other hand, how symptoms such as reduced movement speed and amplitude in PD might result from abnormal movement selection. Moreover, it is not clear how to relate changes in dopamine-dependent habit-learning mechanisms to the motor symptoms of PD. While certain types of learning are impaired in PD,¹⁵ this disorder's clinical symptoms affect quotidian, well-rehearsed movements that are not thought to require new learning.

Part of this difficulty may lie in limitations in our understanding of normal motor control, which has traditionally considered kinematic and kinetic parameters, such as speed and force, to be outside the domain of action selection. Recent work, however, suggests that movement speed may be subject to selection processes analogous to those observed in motivation-driven action selection, and that bradykinesia in PD results from faulty speed selection policies, rather than from an inability to move at normal speeds.¹⁶ This interpretation suggests that movement kinematics are governed by selection processes with their own optimality policies, response to reinforcement, and susceptibility to habit development. Thus the initiation, speed, amplitude, and time course of movements may require circuitry specialised for optimal selection of parameters, similar to the mechanisms that guide action selection and habit learning. The reinforcement signals and optimality policies relevant to motor control may be distinct from those that guide action selection and more complex behaviour, but there may be computational analogies between the selection of *how* to perform a movement (e.g., how soon, how fast, how long) and the selection of *what* movement to perform. Such considerations may extend our understanding of clinical motor symptoms of BG disease that are not explained by current models, and may provide new insights into the BG's more mysterious motor functions. ♦

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Headache in Childhood and Adolescence



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The aim of this review article is to equip you with a paediatric perspective of headache: the commonalities and differences between that seen in childhood and adulthood in terms of presentation, diagnosis and management.

Headache is extremely common in childhood and adolescence. By the age of seven, half of all children will have experienced a headache of one sort or another. Almost all young people will have by the age of 15. The burden of paediatric headache is huge. A recent study showed that 020% of young adolescents suffered from headache which reduced their ability to function for more than 12 days in a three month period and which was associated with reduction in quality of life greater than that of teenagers with diabetes or asthma. Despite this, most young chronic headache sufferers never get to see a headache specialist.¹

History (Figure 1)

Most children and adolescents will attend a consultation with their parents. Involve even the very young patient in the information-gathering part of the visit; a child as young as five can give you a history of pulsating headache aggravated by movement. Parents can provide a perspective on their child's personality, ambitions and worries, all of which can influence the prevalence and experience of headache.²

Examination

In the first article in this series on paediatric neurology Anna Maw discussed the approach to paediatric neurology examination. A detailed neurological assessment by confrontation can be successfully performed in most school-age children, can avoid the need for brain imaging when normal and offer reassurance for patients and parents³. Include:

- Assessment of growth (plot on UK standard growth chart, to include head circumference in a child <4 years).
- Evaluation for meningism, irritability and conscious level.
- Blood pressure measurement.
- Auscultation of scalp and eyes for bruits
- Inspection of mouth for bruxism.
- Bimanual palpation of jaw whilst patient opens and closes mouth.
- Inspection of skin for neurocutaneous syndromes.

Even in the presence of normal neurology however, the presence of 'red flags' should alert you to consider brain imaging or other investigations. Red flags include acute onset of severe headache, headache at night or on waking from sleep with vomiting, or progressive headache with behaviour change and / or academic failure.

Figure 1: Elements of headache history in childhood / adolescence

Headache

- Attack duration, quality, severity, site
- Relationship to posture, coughing etc
- Aggravating and relieving factors: lights, noise, movement, smells, sleep
- Triggers: sleep change, worry, excitement, missed meals, sunshine, caffeine, periods
- Pattern of headache progression

Analgesia + attack treatments: remember medication overuse headache

Related symptoms

- Vagal symptoms including pallor, dark rings, syncope
- Fever, confusion, behaviour change
- Aura: visual aura more frequent but dysarthria + vertigo are common in childhood migraine

Past medical history

- Neonatal / early childhood, eg prematurity related intraventricular bleeding, VP shunt
- History of childhood periodic syndromes
- Obesity (idiopathic intracranial hypertension, obstructive sleep apnoea)
- Blocked nose + facial pain
- Jaw locking / pain on eating, teeth grinding
- Head / neck trauma
- Licit + illicit drug use
- Other systemic disease

Family and social history

- Carefully evaluate family history of 'migraine'
- Family structure and events: factors which provoke or protect against anxiety and depression
- School, academic performance, friends, exercise, ambition, tendency to worry

Secondary headache in childhood and adolescence

The vast majority of secondary headache in childhood and adolescence is associated with other symptoms or examination findings of neurological deficit. Figure 2 highlights some pointers to secondary headaches encountered more commonly in early life.

Figure 2: Important considerations when screening for secondary headaches in childhood / adolescence

Acute severe headache

- *Infection* eg meningitis - the younger the patient the less specific signs of meningism are for meningitis.
- *Venous thrombosis* - headache quality is variable in quality and site with no relationship between site of headache and location of the thrombus save in sigmoid sinus thrombosis. Consider in childhood especially where otitis media / mastoiditis / dehydration are present, or in the presence of hypercoagulable states such as inflammatory bowel disease and nephrotic syndrome. Cranial neuropathies including hemianopia, deafness, oculomotor and abducens palsies are common, with acute raised intracranial pressure signs in lateral sinus thrombosis.
- *Intracranial haemorrhage* - more likely due to bleed into tumour or venous infarct, or from AVM rather than from a berry aneurysm

Acute recurrent headache

- *Idiopathic or symptomatic occipital epilepsy* – post-ictal headache (2/3 of patients) may be indistinguishable from migraine. Unlike migraine, seizures may occur several times a day. A careful history of visual phenomena accompanying headache will be discriminating. With or without blindness, visual hallucinations of occipital seizures usually last 1-3 minutes, are non-progressive, multi-coloured and circular vs the linear, zigzag and dichromatic features of migraine aura. May involve other non-occipital ictal phenomena eg those arising from involvement of temporal lobe.
- *Chiari malformation-related headache* – symptoms attributable to brain protrusion through the foramen magnum include headache, ataxia, vertigo, hearing loss, neck pain and dysarthria aggravated by coughing and Valsalva manoeuvre. Surgical decompression is required for truly symptomatic cases.

Chronic progressive headache

- *Brain tumour* (98% accompanied by other neurology eg eye movement disorder, ataxia).
- *VP shunt blockage / failure* – acute or chronic headache, drowsiness and vomiting all overlap with other common paediatric diagnoses, but a combination of all three in a child with a shunt makes blockage highly likely. An unchanged CT scan does not rule out shunt blockage.
- *Idiopathic intracranial hypertension* – post-pubertal IIH is similar to ‘adult’ IIH with female sex and obesity predominating. In prepubertal children obesity is uncommon; strabismus and a stiff neck may accompany or occur without headache. Opening CSF pressure of >18cmH₂O (age<8y with papilloedema) and >25cmH₂O (age>8 or less than 8 without papilloedema) should suggest IIH in prepubertal children.

Primary headache in childhood and adolescence

Migraine

The most prevalent primary headache in childhood and adolescence, prior to puberty migraine shows early male predominance with 3-11% prevalence. Migraine is more common after puberty (up to a quarter of adolescents) and girls catch up with boys in terms of prevalence. Migraine has been reported in toddlers, behaviour change and vomiting being the predominant symptoms at this age. Spontaneous remission does occur in a large minority of adolescents, with a much reduced chance if migraine is still occurring after 18 years of age. Catamenial migraine is rare in the paediatric population.

IHS criteria for paediatric migraine are different to adult migraine (Figure 3) but the 2-72 hour duration limit is thought to be restrictive as some childhood migraine attacks are very short indeed. Childhood migraine is more likely to be bilateral (bitemporal / bifrontal) compared to adult migraine. Aura occurs in 15%, most commonly visual. Vagal phenomena are often prominent.

Acute confusional migraine is uncommon, with confusion and dysarthria dominating attacks encountered after minor head injury or exercise. This migraine variant, associated with focal slowing on EEG and hypoperfusion on SPECT imaging, can cause considerable diagnostic difficulty at first presentation.

Figure 3: IHS criteria for childhood migraine without aura

Five or more headaches lasting 1-72 hours with at least two of the following characteristics

- Unilateral or bilateral pain
- Throbbing pain
- Moderate or severe pain
- Pain aggravated by routine physical activity

and at least one of the following

- Nausea / vomiting
- Photophobia / phonophobia

The paediatric migraineur may have a history of one or more ‘childhood periodic syndromes’ thought to be migraine variants although there is no clear predictive relationship between many of these and later migraine headache:

- Benign paroxysmal torticollis of infancy (regular attacks of acute agitation, vomiting, pallor and torticollis lasting a few minutes in a toddler).⁴
- Benign paroxysmal vertigo (acute vertigo, nystagmus lasting a few minutes, usually in a pre-adolescent child) – the commonest cause of recurrent childhood vertigo other than recurrent otitis media. The latter is easy to spot by identifying conductive hearing loss and visualising the inflamed eardrum.⁵
- Cyclical vomiting syndrome (incapacitating recurrent vomiting lasting several days sometimes needing hospital admission for fluid support) – strong association with migraine headache and often precipitated by travel, not to be confused with metabolic conditions or Panayiotopoulos seizures.^{6,7}
- Abdominal migraine (periodic headache, pallor and abdominal pain which may be associated with other GI symptoms and fever) – the relationship between this and recurrent abdominal pain of childhood is unclear although they can be delineated by application of the Rome III criteria.⁸
- Recurrent short-lived limb pain in childhood (usually lower limb pain sufficient to prevent usual activities, lasting <72h and not attributable to another cause).⁹

Familial (FHM) and sporadic (SHM) hemiplegic migraine variants have both been linked to channelopathies encoded by mutations in CACNA1A, ATP1A2 or SCN1A genes. FHM mutations have been found in family members with non-hemiplegic migraine.¹⁰ Alternating hemiplegia of childhood is an entirely different condition to FHM / SHM, being an early onset (<18 months) progressive disorder where episodes of alternating and worsening hemiplegia are associated with choreoathetosis and dystonic posturing, progressive developmental delay and episodic ophthalmoplegia (unlike FHM or SHM). Episodes last minutes to hours, are usually precipitated by excitement or tiredness and relieved by sleep.¹¹

Prevention and treatment of paediatric migraine

Composite data from a small number of randomised, placebo-controlled trials show that ibuprofen, nasal sumatriptan / zolmitriptan and oral rizatriptan are effective migraine attack treatments.^{12,13} Preventative therapy has a very poor evidence base in childhood migraine and high quality intervention studies are badly needed. Propranolol and flunarizine have been shown to be effective prophylactic agents, but in only one study each.¹⁴ Pizotifen, amitriptylline, clonidine, nimodipine, anticonvulsants and anti-emetics have not been shown to work although most studies examining these drugs concern small numbers of patients.

Use of complementary therapies for paediatric headache is widespread, and most parents want their clinicians to be able to advise on such therapies even when they do not prescribe them.¹⁵ Despite this, there are no randomised controlled trials for herb-based remedies showing any benefit in childhood migraine. There is no convincing evidence of a link between biogenic amines and migraine but an oligoantigenic diet may benefit severely affected paediatric migraineurs resistant to other treatments. The importance of good sleep hygiene should be emphasised and may be enough for some children's migraines to be prevented without recourse to medication, especially in pre-adolescents. Obesity, like migraine prevalent within the paediatric population, is thought to be a risk factor for chronic migraine but there are no studies as yet which determine the impact of weight loss on migraine frequency in the paediatric population.

Tension type headache

This is a poorly researched primary headache in childhood and adolescence but is probably more common than and at least as debilitating as migraine¹⁶ (Figure 4). Epidemiological evidence from large populations of adolescents with tension-type headache suggest behavioural phenotypes different to migraineurs: a high incidence of anxiety and depression, a tendency to derive stress from academic achievements,^{17,18} association with other somatic symptoms and difficulties with family relationships.¹⁹ Opinion is divided as to whether migraine and tension type headaches represent distinct entities.

Figure 4: IHS criteria for tension-type headache

At least 10 headaches lasting 30 minutes to 7 days with at least two of the following:

- Pressing / tightening quality
- Bilateral location
- Mild or moderate pain (may inhibit but does not prevent daily activity)
- Pain not aggravated by routine physical activity

and both of the following

- No nausea or vomiting
- No photophobia / phonophobia, or one but not the other is present

Prevention and treatment of paediatric tension-type headache

There is no evidence for pharmacological treatment or prophylaxis for childhood tension-type headache although the following may help:

- Limiting analgesic only to the most incapacitating headaches, to avoid medication overuse.
- Cognitive behavioural therapies, for which there is a large evidence base, especially for

biofeedback methods. Group therapies may work.

- Maintain healthy physical exercise and sleep routines.
- Offering to write to a patient's school to encourage a staff response to mild-moderate headache whereby the patient takes prompt analgesia and remains in lessons rather than being sent home. This stops children and adolescents from falling behind socially and academically.
- Manual therapies eg stretching, trigger point release, TENS machine use.
- Topical peppermint / menthol derivatives (4Head, TigerBalm) – no evidence in childhood but a blinded study of adult patients suggests benefit over placebo and similar level of efficacy when compared with paracetamol.²⁰
- Amitriptylline – no evidence for use specifically in this headache type but commonly used where pharmacotherapy sought.

Medication overuse headache

This commonly encountered headache in children and adolescents should always be considered as a potential cause of chronic daily headache. It can occur with almost any headache attack treatment including tryptans, the latter tending to cause medication overuse more quickly than analgesics.²¹ Children and adolescents with medication-overuse frequently respond to medication withdrawal within a month.²²

Short duration headaches

Recurrent headache, lasting seconds to minutes are rare in childhood, and can be difficult to classify according to IHS criteria as features are variable. There is no robust evidence base for management of short duration headache in childhood. Idiopathic stabbing headache is the most widely reported, and in childhood is less likely to be associated with other primary headaches than in adulthood.^{23,24} Like episodic and chronic paroxysmal hemicrania, idiopathic stabbing headache should respond to indomethacin. Cluster headache is rarer still, but as in adulthood appears to be responsive to a range of treatments including oxygen, tryptans, verapamil and dihydroergotamine.²⁵

Summary

This synopsis of paediatric headache shows how much is common to both childhood and adult headaches, but how they differ in presentation, differential diagnosis and treatment. Paediatric headache is the Cinderella of paediatric neurology specialties, but it is worthy of more attention and research, being so common and yet so disruptive to young people's lives. Not before time, the National Institute for Clinical Excellence is now consulting on guidance for new onset headache in adults and adolescents, with guidance for headache in younger children following on in the next few years.

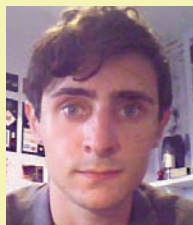
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Neurology And Art: Willem De Kooning



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The extent to which disease interacts with artistic abilities has always been a topic of great interest and in this new series we explore this in the world of art. Many famous artists have suffered from neurological conditions, which in some way have altered their work, whether it be through some alteration in end organ function (e.g. Monet and his eyes) or some more central cause (e.g. Goya). In all cases there is a fascinating and unique insight into the effects of diseases of the nervous system on an individual, and their expression through the evolving and changing visual works produced. In the first article in this new series we consider Willem de Kooning and his work and the effects that his late onset dementia had on this.

Throughout the mid-twentieth century, America became a locus of global cultural activity. Europe, which had previously housed and nurtured the avant-garde within the bohemian setting of modern Paris, had become socially ruptured by World War Two. The Nazi occupation of Paris had left a culture fractured by political disparity, with different facets fighting a philosophical battle over questions surrounding social responsibility. America, meanwhile, was experiencing unprecedented levels of strength. An economic boom impelled the growing consumer society, and capitalist ideology began to lead the world into a new era of commoditisation.

If the brain cannot remember simple events nor hold coherent conversations of thoughts, then how can the art it generates have anything to say?

Contemporary culture found itself disorientated by the rapidly changing bureaucratic structures. The preceding artistic styles of Cubism and Surrealism were underpinned by political ideologies veering on the far-left. In the wake of the war, hope of a communist nirvana had shattered, with Stalin's Russia exemplifying the potential evil of the left wing. For Willem De Kooning and his contemporaries, among them Jackson Pollock, Barnett Newman and Robert Motherwell, art had its most obvious avenues of progression blocked off. These artists, later categorised as the Abstract Expressionists', responded by internalising their artistic concerns, with a privileged emphasis placed on painterly abstraction as the rarified expression of the self. Their aspiration was to enact an unabated interaction with the canvas, sourcing a universal creative drive latent within human consciousness. Motherwell concisely summarised the idea with his assertion that 'painting is...the mind realising itself in colour

and space';¹ Newman augmenting this with his use of shape as a 'vehicle for an abstract thought complex, a carrier of... awesome feelings'.² Stylistically, this led the artists to work on expansive canvases, characterised by a dynamic use of colour. De Kooning was to become the figurehead of Abstract Expressionism par excellence, his popularity in the forties paving the way for others and forming the erudite counterpart to the bohemian explosiveness of Pollock.

Much of the early work of Abstract Expressionism grapples with the transition of the avant-garde from Europe to America, and De Kooning was no exception. *Pink Angels* (1945) with its biomorphic shapes and fluid composition reveals an artist heavily under the influence of Surrealist painter Yves Tanguy. After a series of black and white abstractions, it was in the work *Excavation* (1950) that De Kooning most clearly established a more idiosyncratic style for himself. The work is hardly free of a European and modernistic approach to art; the modulated structure of *Excavation* is highly reminiscent of Cubism whilst the attempt to manifest unconscious thought through unrestrained spontaneity nods to the popularity of Surrealism. Here, however, De Kooning has fused the two into something unique, with the catalyst being a distinctly American sensibility. The title references the new building work undertaken by a newly moneyed

America, with the piece alluding to the symbiosis of emotion between the urban environment of New York and De Kooning's personal response to it. *Excavation* was to galvanise the Abstract Expressionist movement and lead De Kooning to swiftly become one of the premier artists of the day. From this position, we can see how his subsequent return to figurative painting was confusing for people at the time. Nevertheless, it was to yield some of his most celebrated works.

Woman I (1950-1952) took De Kooning two years to complete, having started work on it immediately after the completion of *Excavation*. The final work De Kooning produced was a visceral and disquieting rendering of the female figure, in which a violent use of colour deforms the subject into a snarling animal. Instead of using the urban environment as inspiration, De Kooning focuses on one part of it: the use of the female figure in advertising. Originally starting the piece by painting around teeth from a cigarette advertise-



Willem de Kooning in his studio. Copyright statement: Sam Abell/National Geographic/Getty Images

ment, De Kooning pictorially describes the relationship between the objectified figure and the painter, a subject implicitly framed by the objectification of femininity throughout commercial America. De Kooning's semiotics make explicit the shared unconscious forces at work in each scenario; that of a physical longing overwrought with sexual anxiety, an idea possibly gleaned from the current popularity of Sigmund Freud at that time. In a broader sense, De Kooning's *Woman* decried the end of modernist painting, taking a subject of perennial artistic interest, and imploding it across the canvas. A new era was being ushered in and art was swept along with it, moving away from exhausted conventions and towards pure abstraction. De Kooning, however, mercilessly forged a new identity for traditional painting, the *Woman* series providing the highly charged response to the dilemma faced by art and serving as the nail in the coffin for modernism.

Whilst De Kooning's early abstractions lie at a pivotal point within the vicissitudes of art history, his later works form indexical reference points to an artist clinging to his fading mental faculties. The progression of the artist's Alzheimer's throughout the eighties accompanied abrupt changes in style, raising questions on the extent to which the new works should be considered 'authentic' De Koonings. At the start of the decade, the artist had moved away from some early experimentation with sculpture, to painting untitled abstractions that blended naturalistic hues of colour, seemingly inspired by his new surroundings of East Hampton. Here was an artist staying true to his attempt of '[slipping] into a glimpse',³ taking Monet as a point of departure and dissolving recognisable shapes into an immersive experience of organic colour.

In 1982, De Kooning suddenly began rapidly reducing his style, painting smaller works with far fewer brush strokes. An artist who had taken two years to finish his first *Woman* painting began producing a worryingly high number of works, doubling his work rate in 1983 by completing fifty-four works in just one year. Incidents such as an infamous encounter with the president in which De Kooning did not recognize the American leader (and on being told who he had met afterwards, merely remarked 'gee, I knew he looked familiar') revealed the full severity of his condition. The new work began to garner uniformly bad reviews, with *Time* magazine describing them as 'a lot of banality and parody, conscious or not'.⁴ Yet, De Kooning had not completely lost control of his aesthetic judgment. In 1983 the artist's wife, Elaine, worried that his palette was becoming too limited throughout the proliferation of new works, bought new tubes of paint, which she surreptitiously left with his favoured colours, only to find them unused several weeks later. In some ways then, late paintings by De Kooning exhibit the ultimate extension of the artist's aesthetic theory. The contact with a deep rooted creative force that survived beyond a coherent understanding of the external world, demonstrate the unconscious forces De Kooning contrived to harness in his early life. Critically lauded or not, his last works stand as a testament to the enduring presence of one of the last century's great artists and the creative will of the individual triumphing over its own destitution.

This last phase of his life with its greatly increased output has drawn comments from others,^{5,8} not only as to whether he truly had Alzheimer's disease (AD) (as opposed to depression, Wernicke's encephalopathy, etc)

but also as to the extent to which a brain undergoing a neurodegenerative process can continue to generate meaningful works. If the brain cannot remember simple events nor hold coherent conversations or thoughts, then how can the art it generates have anything to say? Art that takes as its origins some sort of social context for its content cannot surely be regarded as making any profound statement if the author of it has an advancing dementia. Of course disease and its treatment can bring out creativity,^{8,9} but they can also rob it of its content. Does this describe the later works of De Kooning or does his art not require the conscious, cognitive processes stored in those parts of the brain affected by the evolving AD process? We will return to this theme in this series as we consider the lives and neurological conditions of other famous artists. ♦

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Welcome to the third in a series of articles in *ACNR* exploring clinical dilemmas in neuropsychiatry. In this series of articles we have asked neurologists and psychiatrists working at the interface of those two specialties to write short

pieces in response to everyday case-based clinical dilemmas. We have asked the authors to use evidence but were also interested in their own personal views on topics. We would welcome feedback on these articles, particularly from readers with an alternative viewpoint.

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When is an Impulse Control Disorder in Parkinson's Disease a Problem?

Case

A wealthy 61-year-old man has been seen in your clinic for the last seven years with a diagnosis of idiopathic Parkinson's disease. His motor symptoms are well controlled on Ropinirole. At the most recent appointment his wife confides that for the last year she has been distressed by a change in his sexuality. Their sex life had been on the wane but he now had a much higher libido and was requesting sex four or five times a week. He had also uncharacteristically started to buy lottery scratchcards and was spending around £60 a week on these. The patient explained that he enjoyed his scratchcards and his renewed sexual vigour, although was aware that the changes in his behaviour distressed his wife. What do you do?

This case illustrates the intriguing issues that arise from the dopamine agonist (DA)-related impulse control disorders (ICD) reported with Parkinson's disease (PD)¹ and restless legs syndrome.² The ICD behaviours including pathological gambling (5.0%), hypersexuality (3.5%), compulsive eating (4.3%) and compulsive shopping (5.7%) are reported in 13.6% of PD patients in a large North American multicenter study.¹ The ICDs overlap with substance use disorders and are also known as a behavioural addictions.³ These behaviours are associated with DA use, Levodopa presence and higher Levodopa dose.¹ The related behaviours of compulsive dopaminergic medication use are reported in 3%⁴ and punting or hobbyism in 1.5 to 14%^{5,6} and are associated with Levodopa dose.

When is a behaviour considered pathological?

The association between Levodopa and increased sexual drive has long been recognised.⁷ An increase in libido associated with dopaminergic medications, like any other behaviour, exists on a continuum and can be a positive side effect at one end but defined as pathological when it is both a

change from baseline and persistently interferes with social or occupational functioning or is time consuming or distressing.⁸ Hypersexuality commonly presents as excessive requests to the spouse for sex or internet pornography use, less commonly as increased use of prostitutes, and more rarely, paraphilias such as transvestic fetishism. The symptom is commonly discovered on complaint by the patient's spouse to the treating clinicians thus highlighting the hidden nature of the behaviour and the role of family members in diagnosis and management. Notably, hypersexuality in women may be under-recognized as male spouses may be less likely to complain of changes in sexual desire.

Is the patient fully aware of this symptom?

Unlike obsessive compulsive disorder in which symptoms are experienced as excessive or abnormal,⁹ the urge or desire for sex, to eat, gamble or shop associated with DA is commonly experienced as consistent with ones underlying self-image or personality. This experience is more consistent with that of substance use disorders. Hence, insight that the symptom is a problem may be impaired. This lack of insight in substance use

disorders has been suggested to have underlying neurobiological correlates (reviewed in 10).

Is the patient responsible for his behaviour?

In the context of a psychiatric evaluation in the emergency room, a patient presenting with mania (with euphoric or irritable affect, grandiosity, impaired sleep, excessive energy and excessive harmful behaviours including gambling or hypersexuality), would be considered to have diminished responsibility if they did not understand the full consequences of their actions in the context of their illness. Hence, an interim judgment of financial incapacity or treatment incompetence may be relevant. A similar case of impaired judgment and diminished responsibility can also be made for DA-induced pathological gambling. This raises intriguing ethical questions. Primary pathological gambling, unrelated to DA, is not a sufficient condition for consideration of impaired responsibility. The issue can become further confusing. What if an individual has a history of pathological gambling which had been under control prior to the introduction of the DA? DA-induced paraphilias have also been described. Cases of new onset paedophilic behaviour in the context of DA have also been anecdotally described. Is this a disinhibition of a premorbid tendency and if so, is the patient responsible for their behaviour?

Why do some patients develop this behaviour?

DA interacting with an underlying susceptibility (leading to a greater drive towards these behaviours) along with impaired inhibition have been suggested to be the key factors in the pathophysiology of these behaviours. We have shown that specific factors are associated with ICDs in PD. For instance, a family history of gambling problems¹ or alcohol use disorders¹¹ is associated with ICDs, suggesting a potential genetic or social diathesis. A greater association with smoking¹ suggests potential overlaps in neural substrates underlying smoking behaviours and ICDs. That the behaviours are more frequent in unmarried individuals¹ and in the United States as compared to Canada¹ suggests potential cultural or environmental factors. There are gender differences, with hypersexuality more commonly expressed by men and compulsive eating and shopping more commonly expressed by women. A greater association with novelty seeking, impulsivity^{11,12} and faster reward learning¹⁴ suggesting underlying cognitive traits may be similarly affected by DA or play a role in the pathophysiology of the behaviours. Pathological gambling and compulsive medication use in PD may be characterised by greater dopamine release to challenges such as a gambling task,¹³ unexpected reward¹⁴ and Levodopa use.⁴ Imaging studies on hypersexuality have not yet been reported.

Should this be treated?

Patients and their caregivers should be warned about these behaviours as potential medication side effects and actively questioned or administered screening questionnaires¹⁵ during clinic

visits. The behaviours can be presented in the context of other potential side effects thus normalising and increasing the patient's comfort level. Treatment is based on clinical judgment on discussion with the patient and caregiver and depends on balancing the consequences in terms of distress to the patient, spouse or caregiver, other social/occupational dysfunction and time consumed with the tolerance of lower DA doses and motor efficacy of the dopaminergic medications. A high index of suspicion and a careful history is warranted given that the extent of the problem is commonly minimised. A trial of a decrease of DA may be indicated in uncertain cases.

How should this be treated?

Decreasing or discontinuing DA with a concomitant increase in Levodopa appears to be effective with many patients.¹⁶ In patients with comorbid dementia, cholinesterase inhibitors, which can be effective for behavioural symptoms associated with dementia, have also been anecdotally reported to be effective.¹⁷ In patients with comorbid depression, an antidepressant may possibly decrease the obsessional sexual urges.⁸ A family history or a personal history of bipolar disorder may warrant a trial of a mood stabiliser. In severe cases, anti-androgens may be considered.¹⁸ Deep brain stimulation targeting the subthalamic nucleus with a postoperative rapid decrease in dopaminergic dose and DA discontinuation along with active follow up has been reported to be effective for refractory ICDs.^{19,20} Whether this holds for hypersexuality is not clear as post-operative new onset hypersexuality has been clearly reported and ICDs are also associated with an increase in post-operative suicide risk.^{21,22}

How should this particular patient be treated?

Based on the available information in this case, the behaviour is not clearly pathological and may represent a general increase in motivation and libido. However, given the likelihood that the behaviour and degree of distress or conflict is likely minimised, the patient and spouse should be carefully interviewed both separately and together to ascertain the full range of behaviours, frequency, duration, degree of distress and relationship conflict, attempts by the patient to control the behaviour and assessment of other psychiatric symptoms. Careful follow-up, documentation and warnings should be instituted given the risk of escalation of behaviours. If indeed the behaviour and distress is very mild, there is no single correct approach and should be guided by the patient and wife. Understanding that the change in behaviour may simply reflect changes in medication and an improvement back to a pre-Parkinsonian status of motivation and libido along with an increase in communication may be sufficient to alleviate distress. A reasonable approach would be to attempt to behaviourally manage the symptoms in a manner suitable for the couple followed by a trial of a decrease in DA dose if ineffective. ♦

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The ABN Fellowship Scheme: a new opportunity for neurology trainees



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Key Facts on the ABN Clinical Research Training Fellowships

- Open to clinically qualified trainees in neurology and related disciplines
- Provide three year clinical research training fellowships in any neurological discipline
- Additional funding opportunities are available in specific disease areas
- A single application and interview process for all the fellowships
- Salary, university fees, travel costs and laboratory consumables can be funded
- Details of the application process are available at www.theabn.org

Why a new fellowship scheme?

British neurology has a strong academic tradition. A period of time spent in research remains a very valuable part of training for many registrars in neurology. A clinical training fellowship providing up to three years of research funding is the ideal way for trainees to undertake an MD or PhD, which is essential for those considering an academic career. The Medical Research Council and Wellcome Trust offer prestigious fellowships, but these are limited in number and extremely competitive. A number of other charities have traditionally funded training fellowships, but charities have reported increasing difficulties in recruiting suitable candidates and administering the selection process. Some had even considered diverting these funds to other uses. From a trainee's perspective, finding suitable options for funding their research can be a bewildering process, and making multiple applications was extremely time-consuming. Against this background, the Association of British Neurologists recently established a new scheme to coordinate and manage the award of prestigious clinical training fellowships available to neurology trainees from a variety of charitable sources.

How does the scheme work?

The ABN fellowship scheme brings together a number of existing charitable fellowships as well as new funding from the Guarantors of Brain under a single umbrella. This scheme will take place annually and offers opportunities either for fellowships in a non-specified neurological discipline (from the Guarantors of Brain and the Patrick Berthoud Charitable Foundation), or additional opportunities in disease areas sponsored by specific disease-orientated charities. The ABN supports and administers the scheme, including the application, peer review and interview process, but individual charities continue to make the final decisions on which candidate(s) they will fund. A single application form allows applicants to apply for one or more of the fellowships being offered at any one time, depending on their own area of interest, and a single set of interviews is held. The interview panel is appointed by the Clinical Research and Academic Committee of the ABN, chaired by Patrick Chinnery, and includes a member of the Association of British Neurological Trainees

(ABNT) and representatives from each charity offering funding. The process aims to be efficient and streamlined, with a timeline of only 3-4 months between applications and funding decisions. Salary, university fees, reasonable travel costs, and laboratory consumables may be funded, although the resources available from each sponsor differ.

The first round of applications took place in summer 2010, with five fellowships being offered, including disease specific funding from the MS Society, Ataxia UK and the Parkinsons UK. The deadline for applications was the end of May, with interviews held at the end of July and final funding offers made by September. The aim is to repeat the process at a similar time each year, or more frequently if resources become available meanwhile. Full details, including information about the specific fellowships to be offered, are available on the ABN website (www.theabn.org).

How can I make a successful application?

It can take some time to develop a fellowship proposal, so trainees thinking about undertaking research should already be beginning discussions with potential supervisors in time to apply for a fellowship in 2011.

As with the MRC and Wellcome fellowships, the "three Ps" - Person, Project and Place - are all important in the selection process, but a strong emphasis is placed on supporting the career development of the most promising potential academic neurologists. The charities' responsibilities to their trustees means that projects with clear potential benefit to patients are also more likely to be supported. Being well prepared for the interview is essential: candidates need to demonstrate a clear understanding of both the scientific basis of their project and how the fellowship fits into their longer term career plans. Unsuccessful candidates are offered personal feedback at the end of the process with the aim of helping them to make other successful funding applications in future.

In summary, the new ABN Fellowship Scheme should make it easier for neurology trainees to access funding opportunities for research, and aims to offer awards as prestigious as those provided by MRC and the Wellcome Trust. Look out for details of next year's application process on the ABN website. ♦

Immune-Mediated Neuromuscular Diseases

This 16-authored (14 USA, 2 UK) 165 page hardback offering sets out to provide “the latest updates in treatable autoimmune neuromuscular disorders. Due to page limitations, other autoimmune neuromuscular diseases are not discussed. This book contains information about the more common and well-known diseases.”

Is it just me being unkind but would you have been happy with that as the key introductory text on the first page of your book? Putting that aside, does it deliver?

Chapter One: Acute Neuropathies – GBS – five pages including one paragraph (no tables, no graphs, no pictures) devoted to treatment. Five further pages on acute plexopathies, both commenting that there are no RCTs to inform treatment, complete the first chapter.

Let us move swiftly on to Chapter Two Chronic Neuropathies – CIDP and its Variants. Ten pages of text and three pages of references here with two tables bringing a little welcome relief to the eye. Perhaps a page and a

half on treatment at most (again without graphs, tables, or any pictorial imagery) makes this, well, rather dull I’m afraid, which is a pity because within a pretty didactic chapter the thorny issue of how to reconcile the specificity and sensitivity of diagnosis is explored, briefly. The issue of how much or how little clinical or electrophysiological suspicion of CIDP is enough to justify a trial of immunosuppression is touched upon. An evidence-based section on clinically meaningful treatment response would have been a helpful addition.

One gets a more expansive and overlapping look at chronic neuropathies and paraproteins, myeloma, Waldenstroms, and POEMS in a chapter on Dysimmune Neuropathy. Castleman’s gets a mention but from a practical point of view an approach to “treatment-resistant CIDP” is notably absent from either chapter.

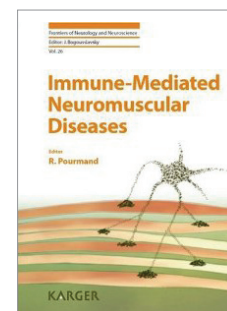
The section on nonsystemic vasculitic neuropathy (40 pages, of which 10 are references) at least contains some attractive photoslides

of the pathology. The pages overflow with more immunopathology than my addled brain can cope with but to their credit the authors do justice to what evidence exists (with references spanning 1914-2009!) regarding treatment (over nine pages) and produce a useful end of chapter summary.

Further topics include autoimmune autonomic ganglionopathy (think I may have seen one once but will be more vigilant now!), myasthenia – AChR and MuskR positive and (double) seronegative, LEMS, idiopathic inflammatory myopathies, and stiff person syndrome.

What does this book have that a large text book or a series of review articles copied or downloaded from journals doesn’t? Convenience perhaps, up-to-date-ness probably, digestibility ‘fraid not.

Aspiring neurologists more drawn to the periphery of the neurological landscape who prefer books with words to journals and computer screens with pictures will like this. Not sure how big that tribe might be... ♦



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Reviewed by:
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Measurement Scales Used in Elderly Care

A Compendium of Tests, Scales, and Questionnaires

The Practitioner’s Guide to Measuring Outcomes after Acquired Brain Impairment

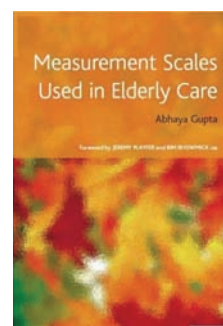
Measurement scales are now ubiquitous in clinical practice, and several compendia of such scales are available. Two recent additions to the market are considered here.

Gupta aimed to write a “handy book for use by a busy clinician”, and to my way of thinking has succeeded. The volume is light, portable, and reproduces most of the scales described. Although aimed principally at geriatricians, there is material here of interest to neurologists and neurorehabilitationists, with scales for coma (GCS), cognition (AMTS, MMSE), stroke, Parkinson’s disease, activities of daily living, and physical disability, amongst others.

Tate’s book is a much more ambitious affair, attempting to map instruments to the components and domains of the 2001 WHO International Classification of Functioning, Disability and Health (ICF) framework, not always an easy task due to the overlap of categories. This mapping may be of more direct relevance to

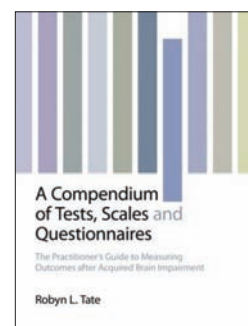
neurorehabilitationists than neurologists; the latter will presumably just pick-and-mix the scales they want according to clinical circumstance. Test descriptions are structured (source, purpose, item description, scale development, administration procedures, psychometric properties, derivatives, comment, and key references) and concise; these are certainly not exhaustive reviews of common tests. For neurologists, the sections on general and specific cognitive functions will probably be of most use.

For the dedicated scale user, meaning some cognitive neurologists, Tate is an extremely valuable and desirable addition to the library, alongside other compendia (e.g. Burns et al., *Assessment Scales in Old Age Psychiatry* 2nd edition, London: Martin Dunitz, 2004), and many neurorehabilitationists will also want to have access to this book as well. For a one-off additional fee (£100), online access to many of the tests can be purchased. ♦



Author: A Gupta
Published by: Radcliffe
Publishing (2008)
Price: £24.95
ISBN: 9781846192661

Reviewed by:
AJ Larner, Cognitive Function Clinic, WCNN, Liverpool, UK.



Author: R L Tate
Published by: Psychology
Press (2010)
Price: £100.00
ISBN: 9781841695617

EDITOR'S CHOICE

Ataxin 2 'premutation' may contribute to ALS

Evidence is accumulating that TDP-43, the hallmark protein of pathological inclusions in ALS, has a direct pathogenic role in motor neurone degeneration. In a recent paper in *Nature*, Elden et al. appear to have identified a protein that may be important in promoting TDP-43 toxicity, and which may influence ALS susceptibility. Beginning with a library of 5,500 yeast genes they characterised 13 genes that suppressed and 27 genes that enhanced TDP-43 toxicity. RNA metabolism appeared to be strongly represented (unsurprising given that TDP-43 has important roles in RNA processing). Although coy about naming these genes, the one candidate they do mention, PBP1, is intriguing as its human orthologue is ataxin 2 (ATXN2), which is mutated in spinocerebellar ataxia 2 (SCA2). Elden et al then show that the human protein, ATXN2, interacts in vitro with TDP-43 and that this interaction is dependent on RNA. Furthermore, post mortem spinal cord examination demonstrated altered distribution of ATXN2 in ALS cases, with the formation of cytoplasmic inclusions. However, TDP-43 and ATXN2 did not appear to colocalise in the spinal cord.

ATXN2 contains a polyglutamine sequence of 22 repeats. Expansions greater than 34 repeats cause SCA2. In a genetic screen Elden et al found that an intermediate repeat number of 27-33 repeats was associated with ALS (24/980 controls had a single allele with such an expansion, while 50/915 ALS cases had this allele). In vitro studies demonstrated that longer repeat lengths increased the stability of ATXN2 and promoted a stronger interaction with TDP-43. Presumably this would increase toxicity. In support of this theory, ALS cases with the expanded repeat length had an earlier age of disease onset (mean age 47.8y) than those with a normal length (59.4y). However, the number of cases that they had sufficient clinical detail to do this analysis on was, curiously, rather small at just 65. As ever, further work is necessary by other groups to replicate these findings.

The search for common genetic variants that contribute to sporadic ALS has been disappointing with conflicting results coming out of most large scale genome wide association studies (GWAS). Chromosome 9p21 has provided the most promising polymorphisms to date, but no mutation has yet been identified (Shatunov et al 2010). Rare genetic variants (immune to analysis by conventional GWAS approaches) are probably more likely to contribute to disease. In identifying and characterising ATXN2 polyglutamine expansions, Elden et al have unearthed what appears to be a very important rare variant. Their toxicity studies in yeast and drosophila suggest that modulation of ATXN2 expression in humans could be a potential therapeutic approach. Research will continue to identify other rare genetic variants associated with sporadic ALS. We are another step closer to the day when we can genetically fingerprint individuals and predict future risk of ALS.

– *Jemeen Sreedharan, Guy's and St Thomas' NHS Trust, London.*

Elsen AC et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. NATURE 2010 Aug 26;466(7310):1069-75.

Shatunov A, et al. Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study. LANCET NEUROL. 2010 Oct;9(10):986-94.

Shining light of what it means to be BOLD

There are now a number of techniques to study brain activity in vivo in patients and normal volunteers including PET scanning, MEG and fMRI. The latter technique relies on the assumption that what is being detected truly reflects neuronal activity, as measured using changes in blood oxygenation level dependent (BOLD) signals. However it is not known whether this is the case, namely exactly what type of local activity causes and accounts for the change in BOLD signal and more specifically can local excitatory neurons give positive BOLD signals. In a recent study this has now been shown using high field fMRI coupled to another new technology which involves activating specific cells using engineered light sensitive ion channels which have been transfected into specific cell types (in this case local CaMKIIalpha-expressing excitatory cells in the primary motor cortex or thalamus) (optogenetics). This technique, called ofMRI, allows for selective cells to be activated when light is shone on them. By looking at the fMRI signal in response to that activation, one can show that e fMRI does equate to neuronal activity in excitatory neurons, and that this activation is pathway specific.

This study is important given that much of what we have learnt from fMRI relies on this assumption and once more demonstrates that our ability to probe neuronal activity in vivo has come a long way since the neurophysiological approaches of the 1960s which defined the beginning of the modern neuroscientific age. Furthermore this new approach not only helps us better understand what changes in BOLD signals actually mean, but ofMRI offers the potential for "global mapping of the causal connectivity of defined neurons in specific brain regions" (p792). As such it may greatly enhance our abilities to dissect the complex circuitry of the brain under a whole host of normal and modelled diseased states.

– *Roger Barker*

Lee JH, et al. Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. NATURE 2010;465:788-92.

Therapeutic trial for non-epileptic attacks – a start at least

Non-epileptic attack disorder is a very common and important clinical problem, and there is little good evidence on how to best manage these patients (confirmed by the most recent Cochrane review on the subject). These authors have published a pilot study, with a view to establishing numbers for a larger, powered trial. The pilot was a randomised, double blind, intention to treat comparison of sertraline versus placebo in patients with non-epileptic attacks in a tertiary centre. The inclusion criteria were: patients aged 18-65, with telemetry evidence of non-epileptic attacks (including patients who also had epilepsy but that could clearly distinguish between attacks). Exclusion criteria were those with subjective sensory attacks, MAOIs, sertraline greater than 100mg, severe psychiatric issues (psychosis, suicidality, substance abuse), litigation or disability application, and those beginning new psychotherapy treatment. Patients were assessed for two weeks and filled in a daily seizure calendar and an assessment battery (including depression and disability scales). Sertraline or placebo was commenced on day 15 and increased bi-weekly to a maximum of 200mg as tolerated. Subjects were reviewed in six bi-weekly sessions and assessed at the end of the study (12 weeks). 128 subjects were assessed for inclusion, 90 excluded, 38 randomised (19 to sertraline, 19 to placebo) with 17 and 16, respectively, analysed. Drop-outs were largely due to patients' concerns about receipt

of placebo rather than active drug. The primary outcome was relative change in seizure rates: those in the sertraline group had a 45% reduction in seizures (placebo 8% increase) and 8/17 had a 50% reduction in seizure frequency (placebo, 3 of 16) (NNT 3.53). The statistical comparisons were non-significant. There were no differences in secondary outcomes, including depression.

The authors concluded that sertraline was producing its effect directly through serotonergic modulation rather than via an antidepressant effect. An antidepressant effect should probably be seen at 12 weeks, but a longer follow up may be more informative. The numbers were too small to be able to make such inferences. The authors felt that since even low doses of sertraline produced improvement in seizure control, patients with non-epileptic attacks have a lower serotonin response threshold; yet, 50% of subjects were taking antidepressants (no information was provided on which types) before enrolment and the authors felt that increasing the dose would produce a therapeutic effect. There were also some patients taking anti-epileptics but the patients were clear they were taking them for other indications such as mood stabilisation or migraine.

The authors found that most participants had more than one Axis 1 psychiatric disorder, so suggested not excluding patients with psychiatric disorders from such trials but instead stratifying according to personality disorders. I would agree with this given that patients with personality disorders have a higher rate of factitious disorder (as opposed to functional disorders). This paper provides useful information to guide further trials in non-epileptic attacks, an area sorely in need of further study, and the disorder is certainly common enough to allow comprehensive trials to take place.

– **Wendy Phillips, Neurology Unit, Addenbrooke's Hospital, Cambridge, UK.**

LaFrance et al. Pilot pharmaceutical randomised controlled trial for

psychogenic nonepileptic seizures. NEUROLOGY 2010;75:1166-73

(epub Aug 25)

When is an AED not an AED? The ups and downs of inhibition in epilepsy

It has been known for some years that the behaviour of GABA receptors changes during maturation, because of differences in subunit composition. In mature neurons, the receptor allows influx of chloride ions, causing hyperpolarisation and reducing excitation of the post-synaptic cell. However, in immature neurons, higher levels of chloride and different properties of the receptor mean that they cause efflux of chloride resulting in excitation, which has a role in neuronal migration and synapse development. Clearly, this has implications for the use of anti-epileptic drugs acting via GABA receptors, such as benzodiazepines, in early life. In this study the authors looked at the property of neurons removed at epilepsy surgery in 25 children with areas of cortical developmental abnormality and the properties of neurons, mostly removed at post-mortem from 20 children without epilepsy. In normal individuals, the expression of GABA α 1 and γ 2 subunit expression increased over the first five years of life before reaching a plateau. The normal brains also exhibited changes in the relative proportions of chloride transporters, NKCC1 (decreases after birth) and KCC2 (increases from low levels with maturation). In the

EDITOR'S CHOICE

Multiple Sclerosis: treating with anti-hypertensive drugs

Traditionally viewed as being pivotal for blood pressure regulation and fluid homeostasis, the renin-angiotensin-aldosterone system (RAAS) and specifically the angiotensin-converting enzyme (ACE) - angiotensin II - angiotensin II type 1 (AT1) receptor axis have now also been suggested to play an important role in tissue inflammation and fibrosis. T-cell expression of the AT1 receptor has been suggested to contribute to both inflammatory events and the development of hypertension. Moreover, activated T cells themselves generate angiotensin II to influence cell function in an auto- and paracrine fashion, and ACE inhibitors suppress inflammatory CD4+ T cell subset development (Th1 and Th17 cells) and induce regulatory immunosuppressive T cell subsets (Treg). In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), AT1 expression in the CNS is increased and subsequent AT1 receptor blockade using candesartan or losartan or by ACE inhibition using lisinopril ameliorates the autoimmune inflammation. Similarly, proteomics analyses of MS plaques indicates a presence of proteins related to the RAAS (Platten et al PNAS 2009). However, the explanation for the anti-inflammatory properties of AT1 receptor or ACE inhibitors remained largely unknown.

In a recent paper, also from Larry Steinman's group, an intriguing network of regulations was unravelled, suggesting an explanation for the pro-inflammatory properties of angiotensin II. The researchers were able to show in EAE that angiotensin II acts on CNS-resident astrocytes and microglia, which respond by an increase in secretion of the cytokine transforming-growth factor beta (TGF-beta) and its activating enzyme thrombospondin-1. This connection between angiotensin II and TGF-beta was not entirely unknown, as angiotensin II-dependent induction of TGF-beta is pathophysiologically connected with pulmonary, cardiac and renal fibrosis. An increase in TGF-beta can have pleiotropic functions in the immune system, with sometimes opposite outcomes; it is able to suppress inflammation but in different situations it can also exacerbate inflammation. The function seems to be dependent on the surrounding tissue and the interplay between different mediators. In respect to the entire organism, systemic applications of TGF-beta show immunosuppressive functions. However, paradoxically, the blockade of the TGF-beta production in the CNS leads to an amelioration of inflammatory reactions and a clinical remission in the MS animal model. Lanz et al were able to show that AT1 receptor blockade by losartan is able to inhibit the inflammatory-induced elevated TGF-beta concentrations within the CNS, which contribute to uphold neuroinflammation. However, TGF-beta basal levels, which are continuously produced in the brain, were not changed. This suggests that interventions into the RAAS do not alter basic immune responses but rather inhibit harmful elevations of TGF-beta. So far no increase in risk of opportunistic infections under RAAS interventions has been reported.

Although this and previous studies advocate the possible beneficial role of the antihypertensive and licensed AT1 receptor or ACE inhibitors for the treatment of MS, the situation in humans might be considerably different from that seen in the experimental mouse models. Here, the therapy was only effective in mice when the treatment was started before the animals developed any paresis: an unlikely clinical situation. While there remain concerns about the effectiveness of these drugs in human MS the long standing clinical experience and their well described side effects do, in my opinion, justify clinical studies using AT1 receptor or ACE inhibitors in MS.

– **Manuel A Friese, University Medical Centre, Hamburg, Germany, Lanz TV, et al. Angiotensin II sustains brain inflammation in mice via TGF-beta. JOURNAL OF CLINICAL INVESTIGATION 2010 Aug 2; 120(8):2782-94.**

epileptic cortex, the maturation of GABAA subunit types was not seen but instead there were patterns of expansion unique to each patient. Similarly there was not the normal maturation of chloride transporters in epileptic brains. What does this mean? Firstly, it may be one explanation of inter-patient variability in the anti-epileptic effect of AED, not only in paediatric epilepsy, but if these patterns are maintained, also in adult epilepsy. The challenge now is to identify these patients and predict AED response, without having to do a biopsy

– **Mark Manford, Neurology Unit, Addenbrooke’s Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**
Jansen LA, et al. Impaired GABA maturation of cortical GABAA receptor

Epilepsy: not just seizures

Over the years, a number of studies have compared epilepsy with other chronic conditions with respect to the impact of the condition on psychosocial status and broader health-related outcomes. This large study looked at the Canadian population, using the Canadian Community Health Survey (CCHS), which is administered to a large representative sample of the population. Certain individuals are excluded; the armed forces, those living in Indian Reserves and some in remote regions. In this study the characteristics of patients with epilepsy (prevalence 0.6%), diabetes (prevalence 3.6%) and migraine (prevalence 8.4%) were compared. Numerous variables were studied and the relevant ones, which showed some differences between groups, are in the table below. The diabetes data are the least comparable because of the difference in the age of patients and the specific nature of the risk factors for diabetes, e.g. BMI. The social disadvantage of patients with epilepsy is striking. The study does not tell us who was in employment or whether some of the low income amongst epilepsy patient may have been benefits rather than earned income, and potentially an even more striking disparity. Although patients with epilepsy were more likely to be smokers than the general population (28.1% v 23.6%), this difference disappeared when the data were adjusted for age, income, gender and education. Alcohol consumption appeared bimodal in all groups with over half of patients never drinking and the second largest group consuming over 12 units per week; 25% of epilepsy sufferers, compared with 18.2% of the general population. The association of epilepsy with thyroid disease and with colitis is unexplained.

	General popn	Epilepsy	Migraine	Diabetes
	400,000	2,555	37,797	22,432
Median age	44	43	40	64
Female	50.7%	50.9%	71.4%	46.9%
Married/partner	58.4%	48%	59.7%	67.6%
Single	29.9%	38.4%	28.2%	9.8%
University education	36.6%	26.9%	32.9%	30.2%
Income (Canadian Dollars)	32,857	22,807	28,353	27,706
BMI > 30	15.4%	20%	18%	37%
Physical inactivity	50%	60%	50%	
Thyroid disease	5.3%	9.1%	7.6%	10.8%
Arthritis	16.2%	23.9%	22.7%	37.8%
Stroke	1.1%	5.6%	1.5%	5%
Crohn’s disease/colitis	2.8%	5.5%	6.1%	4.4%
Asthma	8.4%	12.3%	14.8%	10.1%

– **Mark Manford, Neurology Unit, Addenbrooke’s Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**
Hinnell C et al. Health status and health-related behaviors in epilepsy compared to other chronic conditions – a nation population-based study.
EPILEPSIA 2010;51:853-61.

Cognition in PSP and MSA

The Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study represents the largest prospective cohort of PSP and MSA patients (> 750) yet evaluated, with high overall clinical diagnostic accuracy (94%) compared to pathological examination (n = 112; see also Brain 2009; 132:156-171). This cohort has therefore provided an opportunity to examine the cognitive phenotype of these conditions, assessed using the MMSE, Frontal Assessment Battery (FAB), and Mattis Dementia Rating Scale (DRS) in 372 MSA patients and 311 PSP patients, most (> 80%) receiving levodopa preparations. MMSE and FAB scores were higher in the MSA group. On the DRS, PSP patients were worse on all global and age-scaled subscale scores, with the means for the MSA group being close to the population average for each subscale. Overall, 57% of PSP patients and 20% of MSA patients were judged impaired, with an identical cognitive profile, the main impairment being in the Initiation and Perseveration subscale, especially for the verbal fluency item. Only about one-fifth of PSP patients but two-thirds of MSA patients showed no impairment in any cognitive domain.

My education, dating to the last century, was to the effect that cognitive impairment was extremely rare in MSA, and indeed some suggested diagnostic criteria have regarded cognitive impairment as an exclusion criterion for the diagnosis. This large prospective cohort study clearly shows this to be an error, which will need to be addressed in future clinical diagnostic criteria. Moreover, cognitive as well as motor endpoints might now be regarded as reasonable outcome measures in any future therapeutic trials of disease-modifying agents in these conditions.

– **AJ Larner, Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool, UK.**
Brown RG, et al.
Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy.
BRAIN 2010;133(8):2382-93.

Valproate, levetiracetam or both for Down syndrome with cognitive decline and myoclonus

These authors reviewed the records of all patients referred to their centres with Down syndrome. They found 18 patients with adult onset of myoclonic jerks. The age of onset of cognitive decline as described by carers ranged from 36-59 years (mean 48). Massive myoclonic jerks were initially prominent in all patients soon after waking and sometimes they presented with falls as a result. As the dementia progressed, the jerks became prevalent throughout the day. Fourteen patients also had tonic clonic seizures, mostly after, but sometimes before the onset of myoclonus. EEG’s showed widespread slowing in all and generalised spike and wave in ten of the patients. Treatment with valproate or levetiracetam or both together seemed to have the best effect. Other agents were also tried in more refractory patients with variable success. These patients crop up from time to time in all our clinics; it is good to know of others’ experiences.

– **Mark Manford, Neurology Unit, Addenbrooke’s Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**
De Simone R, et al.
Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer’s Disease in Down syndrome.
SEIZURE 2010;19:383-9.

Can I smoke dope Doc?

The MS doctors have been grappling with this question for a number of years and it does come up in the epilepsy clinic from time to time. My usual response of: “not in the waiting area”, is perhaps not the most constructive but it does highlight the illegality of these drugs. There is of course the broader philosophical question around cannabinoids in a society that enjoys alcohol to the point where one in five male admissions to hospital is alcohol related, and where doctors dish out opiates like Smarties®, but perhaps I should come off my hustings and look at

some science. This is one of a series of studies which has looked at cannabinoids over the years. Most have looked at the hippocampus in partial epilepsy and have found that changes in cannabinoids are generally consistent with them having an anti-epileptic role. These authors studied a genetic model of absence epilepsy, in which rats develop absence seizures at three months of age. Various brain regions were analysed for cannabinoid CB1 and animals were also analysed with EEG. Data showed a reduction in CB1 receptor mRNA and protein levels as control rats matured in a range of brain areas, with the most marked difference between control and epileptic rats being a much greater reduction in the thalamic reticular nucleus, believed to be involved in thalamocortical circuits, important in absence epilepsy. Injecting rats with an agonist at this receptor had complex effects on spike-wave discharges but the most significant was a reduction in discharges in the first two hours, which was blocked by an antagonist at the same receptor. So when my patients tell me that dope is the only thing that helps their seizures, do I believe them? Of course I do. When they ask if it is OK for them to smoke it, I mumble something vaguely disapproving yet permissive. Will we ever prescribe cannabinoids for epilepsy? Perhaps, if the clinical evidence is good enough. We are lucky that in MS, the evidence is sufficiently poor that it plays into public prejudices and political priorities. It will take a brave pharma to try and bring a cannabinoid to market in a climate where politics and scientific evidence combine in decision-making like oil and water.

– **Mark Manford, Neurology Unit, Addenbrooke's Hospital, Cambridge, and Bedford Hospital, Bedford, UK.**

Van Rijn C et al.

WAG/Tij rats show a reduced expression of CB1 receptors in thalamic nuclei and respond to the CB1 receptor agonist, R9+) WIN55,212-2, with a reduced incidence of spike-wave discharges.

EPILEPSIA 2010;51:1511-21.

MS: glutamatergic neuroprotection?

Glutamate mediated excitotoxicity has long been thought a mechanism of neuronal damage in MS, demonstrated for example by the amelioration of EAE with an AMPAR antagonist by Cedric Raine's group (Pitt et al Nature Medicine 2000), correlation of glutaminase with axonal damage in MS lesions (Werner et al Ann Neurol 2001), and MR spectroscopic measures of raised glutamate in acute MS lesions and normal appearing white matter (Srinivasan et al. Brain 2005). Looking for associations of polymorphisms in genetic regions which control glutamate processing has already proven interesting, and favours the established view that raised glutamate overall is associated with accelerated neuronal loss, as measured by brain volume (Baranzini et al. Brain 2010). So it is with interest to see a report that asks us to think of glutamate's potential for good. The model is thus: glutamate encourages dendritic cells in an inflammatory environment to produce a cytokine milieu that pushes T cells away from a pro-inflammatory lineage (Th17) towards a protective one (Treg). The mechanism is through activation on dendritic cells of the type III metabotropic glutamate receptor, mGluR4, erstwhile known to be predominantly presynaptic and highly expressed in cerebellum and olfactory bulb (Pekhletski et al. J Neurosci 1996). Here, mGluR4 knockout mice exhibit earlier onset and more severe MOG35-55-induced EAE than wild type, with a greater influx of inflammatory cells on histology, and an mGluR4 positive allosteric modulator (PAM) rescues EAE in wildtype mice but not in the knockouts. The implementation of all this, through trials of specific PAMs of mGluR4 and therefore ensuring a highly selective action, may be tricky, and if the effect is just on inflammation, then why develop another anti-inflammatory drug for MS at all? As an adjunct with immediate efficacy is one possible answer.

– **Mike Zandi, Fallarino et al. Metabotropic glutamate receptor-4 modulates adaptive immunity and restrains neuroinflammation. NATURE MEDICINE 2010Aug;16(8):897-902. And editorial by Hansen and Caspi, page 856-8.**

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European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Annual Meeting

Conference details: 13-16 October; Gothenburg, Sweden. Reviewed by: Susan Mayor, Freelance Medical Journalist

Encouraging findings from clinical trials with new oral disease-modifying agents being developed to treat multiple sclerosis (MS), further evidence from epidemiological studies on the role of vitamin D status in the risk of developing MS and a greater emphasis on understanding MS in children were key themes emerging at this year's European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) annual meeting.

Swedish study confirms MS link with low exposure to ultraviolet radiation

Low exposure to ultraviolet (UV) radiation is associated with increased risk of developing MS among both women and men, according to latest results from the ongoing Epidemiological Investigation of MS (EIMS). This is a population-based case-control including the general population aged 16-70 years in defined areas of Sweden.

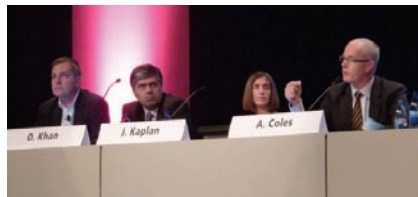
Results based on 1231 incident cases of MS and 2682 controls showed that people with the lowest previous UV exposure had nearly twice the risk of developing MS compared to those reporting the highest exposure (odds ratio 2.0, 95% confidence interval 1.4-2.7). There was a statistically significant inverse trend – the lower UV exposure, the higher risk of MS. Vitamin D levels were significantly lower among cases than controls ($p=0.04$), with a significant inverse trend between levels of vitamin D and MS. The research group found no association between exposure to UV radiation and vitamin D levels and HLA-DRB1*15.

Reporting the findings, the group from the Karolinska Institute, Stockholm, said, "Low exposure to ultraviolet radiation is associated with an increased risk of developing MS among both women and men. Together with the observed association between vitamin D and MS, these findings support the hypothesis that vitamin D is causally related to risk of MS."

Canadian study in children with acute demyelination reveals MS risk factors

Vitamin D levels and the HLA-DRB1*15 allele are independent risk factors for MS in children, show new results from the Canadian Pediatric Demyelinating Disease Network. The study included 332 children (aged under 16 years) with acute demyelination recruited from 23 sites across Canada and monitored prospectively with serial clinical and MRI visits. During follow-up, MS was diagnosed in 63 children (19%).

Results revealed that children carrying at least one copy of the HLA-DRB1*15 allele had nearly three times the risk of developing MS than those without (hazard ratio 2.84). Children of European ancestry showed partic-



ularly high risk of developing MS if they carried the allele. In a preliminary subgroup of 83 children, in which 19 (23%) were diagnosed with MS; DRB1*15 carriers had more than a ten-fold risk (HR 10.57) compared to noncarriers.

Increasing levels of serum 25-dehydroxy vitamin D were associated with reduced risk of MS, with a hazard ratio of 0.87 for each 10nmol/l increase. Mean 25-(OH) D levels within 40 days of the onset of symptoms were lower in children that went on to develop MS (mean 52 nmol/l) than in those that did not (66.2nmol/l) ($p=0.004$).

Heather Hanwell, from the University of Toronto, told the meeting, "Paediatric MS is not nearly as rare as we thought; three to ten per cent of MS cases begin to experience clinical signs and symptoms in childhood and adolescence." She added, "The HLA-DRB1*15 allele and circulating 25-dehydroxy vitamin D levels are independently associated with MS diagnosis following acute demyelination in children. Further study is justified to determine whether improving vitamin D status from conception through childhood will reduce MS risk."

Five year follow-up data show alemtuzumab achieves sustained reduction in relapses and disability in multiple sclerosis

Patients with multiple sclerosis (MS) treated with alemtuzumab show sustained reduction in relapses and disability after five years, according to results reported at ECTRIMS. The CAMMS223 study randomised 334 patients with early, active relapsing remitting MS to alemtuzumab (at doses of either 12mg/day or 24mg/day) for up to five days in two or three cycles, or to interferon beta-1a (44mcg, three times/week).

Results after five years of follow-up showed consistently lower annualised relapse rates in patients treated with alemtuzumab (0.11) compared with those randomised to interferon beta-1a (0.35). Only 13% of patients in the alemtuzumab group demonstrated sustained increase in disability, compared with 38% of those taking interferon beta-1a.

"These long-term follow-up data suggest that alemtuzumab may have a significant disease modifying effect in patients with early, active, relapsing-remitting MS," said Dr Alasdair Coles, Senior Lecturer, University of Cambridge, UK, and lead investigator of the study. He added,

"The efficacy after five years is as good as we saw after three years, despite patients being given no more treatment with alemtuzumab, so we are seeing a durable effect."

Further results for patients with highly active relapsing remitting MS in the study (just over half of those taking part) showed the annualised relapse rate was reduced by 81% in those treated with alemtuzumab (0.09) compared to those treated with interferon beta-1a (0.47), after three years' follow-up. 91% of alemtuzumab-treated patients were free of sustained accumulation of disability, compared to 75% of those in the comparator group. These patients all had highly active disease, with at least two relapses in the year before treatment in the trial, and at least one gadolinium enhancing brain lesions identified by magnetic resonance imaging.

Two phase 3 trials are currently further evaluating alemtuzumab in the treatment of MS, with results expected in 2011.

Global study confirms increase in MS in women

The ratio of women developing MS compared to men has increased over the last 60 years, revealed results from the MSBase Registry. Researchers identified cases of definite MS with birth years ranging from 1930 to 1989 through the international registry and calculated the female to male sex ratios. Figures were adjusted to take account of any differences in the birth rates for each country, using national birth registers.

Results for the whole population of 11,028 patients showed a progressive increase in the adjusted female/male sex ratio from the first to the last decade, from 1.78 to 2.96 ($p<0.05$ for the trend). This increase was more pronounced in northern countries, where the sex ratio increased from 1.93 to 4.55 ($p<0.0001$ for the trend).

"The results confirm a worldwide increase of the female/male sex ratio among MS patients, and demonstrate a greater increase in northern countries. These data seem to suggest a general increase of MS incidence with a significant influence of gender-related and environmental factors," said G. Graziano, from the MSBase Registry Research Group.

Teriflunomide significantly reduces relapse rate and disease progression in relapsing MS

Further encouraging news with oral disease-modifying agents were reported in results from the phase III TEMSO study showing that teriflunomide significantly reduced relapse rate and disease progression in patients with relapsing MS.



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RRMS: relapsing–remitting multiple sclerosis. DMD: disease-modifying drug. sc: subcutaneous. tiw: three times weekly. im: intramuscular. qw: once weekly.

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REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
 REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
 REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE
 REBIF® 8.8 MICROGRAMS AND 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
 REBIF® 22 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
 REBIF® 44 MICROGRAMS SOLUTION FOR INJECTION IN PRE-FILLED PEN
 REBIF® 8.8 MICROGRAMS/0.1ML AND REBIF® 22 MICROGRAMS/0.25ML SOLUTION FOR INJECTION IN CARTRIDGE
 REBIF® 22 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE
 REBIF® 44 MICROGRAMS/0.5ML SOLUTION FOR INJECTION IN CARTRIDGE

Interferon beta-1a

Presentation Rebif 8.8µg and 22µg: Pre-filled glass syringe containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Pre-filled glass syringe containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg and 22µg: Disposable pre-filled pen injector (RebiDose) containing 8.8µg or 22µg of Interferon beta-1a in respectively 0.2 or 0.5ml. Rebif 22µg or 44µg: Disposable pre-filled pen injector (RebiDose) containing 22µg or 44µg Interferon beta-1a in 0.5ml. Rebif 8.8µg/0.1ml and Rebif 22µg/0.25ml: Pre-filled glass cartridge containing 132µg of Interferon beta-1a in 1.5ml. Rebif 22µg/0.5ml or Rebif 44µg/0.5ml: Pre-filled glass cartridge containing 66µg or 132µg of Interferon beta-1a in 1.5ml. **Indication** Treatment of relapsing multiple sclerosis. Efficacy has not been demonstrated in patients with secondary progressive multiple sclerosis without ongoing relapse activity. **Dosage and administration** Initiate under supervision of a physician experienced in the treatment of multiple sclerosis. Administer by subcutaneous injection. Recommended dose: Weeks 1 and 2: 8.8µg three times per week (TIW); weeks 3 and 4: 22µg TIW; week 5 onwards: 44µg TIW (22µg TIW if patients cannot tolerate higher dose). RebiDose pre-filled pen is for single use and should only be used following adequate training of the patient and/or carer. Follow the instructions provided in the package leaflet. Rebif solution for injection in cartridge is for multidose use and should only be used with the RebiSmart autoinjector device following adequate training of the patient and/or carer. Follow the instructions provided with the RebiSmart device. Limited published data suggest that the safety profile in adolescents aged 12–16 years receiving Rebif 22µg TIW is similar to that in adults. Do not use in patients under 12 years of age. Prior to injection and for 24h afterwards, an antipyretic analgesic is advised to decrease flu-like symptoms. Evaluate patients at least every second year of the treatment period. **Contraindications** History of hypersensitivity to natural or recombinant interferon beta, or to any of the excipients; treatment initiation in pregnancy; current severe depression and/or suicidal ideation. **Precautions** Inform patients of most common adverse reactions. Use with caution in patients with previous or current depressive disorders and those with antecedents of suicidal ideation. Advise patients to report immediately any symptoms of depression and/or suicidal ideation. Closely monitor patients exhibiting depression and treat appropriately. Consider cessation of therapy. Administer with caution in patients with a history of seizures and those receiving anti-epileptics, particularly if epilepsy is not adequately controlled. Closely monitor patients with cardiac disease for worsening of their condition during initiation of therapy. Patients should use an aseptic injection technique and rotate injection sites to minimise risk of injection site necrosis. If breaks in skin occur, patients should consult their doctor before continuing injections. If multiple lesions occur, discontinue Rebif until healed. Use with caution in patients with history of significant liver disease, active liver disease, alcohol abuse or increased serum ALT. Monitor serum ALT prior to the start of therapy, at months 1, 3 and 6 and periodically thereafter. Stop treatment if icterus or symptoms of liver dysfunction appear. Treatment has potential to cause severe liver injury including acute hepatic failure. Full haematological monitoring is recommended at months 1, 3 and 6 and periodically thereafter. All monitoring should be more frequent when initiating Rebif 44µg. New or worsening thyroid abnormalities may occur. Thyroid function testing is recommended at baseline and if abnormal every 6–12 months. Use with caution in, and closely monitor patients with, severe renal and hepatic failure or severe myelosuppression. Serum neutralising antibodies may develop and are associated with reduced efficacy. If a patient responds poorly and has neutralising antibodies, reassess treatment. Use with caution in patients receiving medicines with a narrow therapeutic index cleared by cytochrome P450. Women of childbearing potential should use effective contraception. Limited data suggest a possible increased risk of spontaneous abortion. During lactation, either discontinue Rebif or nursing. If overdose occurs, hospitalise patient and give supportive treatment. **Side effects** In the case of severe or persistent undesirable effects, consider temporarily lowering or interrupting dose. **Very common:** flu-like symptoms, injection site inflammation/reaction, headache, asymptomatic transaminase increase, neutropenia, lymphopenia, leucopenia, thrombocytopenia, anaemia. **Common:** injection site pain, myalgia, arthralgia, fatigue, rigors, fever, pruritus, rash, erythematous/maculo-papular rash, diarrhoea, vomiting, nausea, depression, insomnia, severe elevations of transaminase. **Serious side effects include:** injection site necrosis, hepatic failure, hepatitis with or without icterus, severe liver injury, anaphylactic reactions, angioedema, erythema multiforme, erythema multiforme-like skin reactions, seizures, thromboembolic events, thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome, suicide attempt, Stevens–Johnson syndrome, dyspnoea, retinal vascular disorders. Consult the Summary of Product Characteristics for more information relating to side effects. **Legal category** POM. **Price** Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) syringes – £552.19. Rebif 22µg: 12 syringes (0.5ml) – £624.77. Rebif 44µg: 12 syringes (0.5ml) – £813.21. Rebif 8.8µg and 22µg: 6 (0.2ml) + 6 (0.5ml) pens – £552.19. Rebif 22µg: 12 pens (0.5ml) – £624.77. Rebif 44µg: 12 pens (0.5ml) – £813.21. Rebif 8.8µg/0.1ml and 22µg/0.25ml: 2 cartridges – £406.61. Rebif 22µg/0.5ml: 4 cartridges – £624.77. Rebif 44µg/0.5ml: 4 cartridges – £813.21. For prices in Ireland, consult distributors Alphar Services Ltd. **Marketing Authorisation Holder and Numbers** Merck Serono Europe Ltd, 56 Marsh Wall, London, E14 9TP; EU/1/98/063/007; 003; 006; 017; 013; 016; 010; 008; 009. **For further information contact:** UK: Merck Serono Ltd, Bedford Cross, Stanwell Road, Feltham, Middlesex, TW14 8NX. Tel: 020 8818 7373. **Republic of Ireland:** Merck Serono, 4045 Kingswood Road, Citywest Business Campus, Dublin 24. Tel: 01 4687590. **Date of Preparation** July 2010.

Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. In the Republic of Ireland information can be found at www.imb.ie. Adverse events should also be reported to Merck Serono Limited - Tel: +44(0)20 8818 7373 or email: medinfo.uk@merckserono.net.

References:

1. PRISMS Study Group. *Lancet* 1998;**352**:1498–1504.
2. Kappos L *et al.* *Neurology* 2006;**67**:944–953.
3. Steinberg SC *et al.* *Clin Drug Investig* 2010;**30**(2):89–100.

Date of Preparation: August 2010 REB10–0231

Teriflunomide blocks de novo pyrimidine synthesis, which inhibits the replication and function of activated, but not resting, lymphocytes. The study randomised 1,088 patients with relapsing MS to teriflunomide (7mg or 14mg) or placebo, once daily for 108 weeks.

Results showed that both doses of teriflunomide reduced the primary endpoint of annualised relapse rate (ARR) by 31.2%, from 0.539 with placebo to 0.37 with the 7mg dose and to 0.369 with the 14mg dose. There was also a significant increase in the time to first relapse of 29.8% with the higher dose of teriflunomide, and a 30% reduction in disability progression. In addition, MRI shows significant reduction in disease activity with active treatment.

“This is somewhat happy news,” said Paul O’Connor, from the University of Toronto, Canada, as he reported the findings. He noted that teriflunomide was well tolerated with a similar number of patients reporting adverse events as with placebo. Nausea, diarrhoea and minor hair thinning were more common with active therapy. “Altogether, these observations indicate that teriflunomide is a safe and effective new oral monotherapy for relapsing MS,” he concluded.

Study confirms anti-JCV antibodies in natalizumab-treated patients developing PML

Around half of MS patients treated with natalizumab have antibodies to JC virus (JCV), according to results from the largest cohort yet to look at this issue. JCV infection is one of the key factors necessary for the development of PML, so detection of anti-JCV antibodies in blood may be a useful tool to identify previous or ongoing JCV infection in order to stratify PML risk in MS patients treated with natalizumab.

A novel two-step enzyme-linked immunosorbent assay (ELISA) was used to detect anti-JCV antibodies in blood from natalizumab-treated patients enrolled in TYSABRI safety studies. A chi-square test was used to assess associations between factors and prevalence of anti-JCV antibodies.

Results showed a seropositivity rate of 48.0%. There was an increasing prevalence of anti-JCV antibodies in men compared to women. There was also an increasing prevalence with age, regardless of gender. Treatment with natalizumab and prior treatment with immunosuppressants did not appear to affect the prevalence of anti-JCV antibodies.

Reporting the findings, Meena Subramanyam, from Biogen Idec, said, “Together, these data represent one of the largest cohorts of MS patients evaluated for the presence of anti-JCV antibodies, demonstrating an overall prevalence of anti-JCV antibodies of approximately 50 to 60% and delineating the prevalence by factors such as age and gender.”

He noted that large, prospective clinical studies are underway to expand on previous observations that antibodies to JCV were detected in all 17 of 17 MS patients prior to being diagnosed with progressive multifocal leukoencephalopathy (PML), to determine the potential utility of the ELISA test to stratify PML risk in natalizumab-treated patients.

Survey suggests healthcare professionals may underestimate mobility loss in MS patients

Healthcare professionals may underestimate the extent of mobility impairment in patients with MS, according to a new survey. The survey, commissioned by Biogen Idec, of 180 healthcare professionals from Canada, France, Germany, Spain, Sweden and the UK showed that 56% considered that their MS patients experience some loss of mobility, which is lower than published data which suggest up to 85% of people with MS suffer impaired mobility.

A second survey of 436 MS patients illustrated the impact of impaired mobility. Almost three-quarters (72%) said their mobility problems had had significant impact on their working lives and nearly two-thirds (64%) had lost earnings due to MS-related mobility issues.

Professor Shibeshih Belachew, from the University of Liege, Belgium, said, “Loss of mobility can have a huge impact on all aspects of life for patients living with MS. It has physical and psychological effects that can drastically reduce patients’ ability to work.” He suggested that the survey findings indicate the need for greater dialogue about mobility issues between patients and healthcare professionals. Mobility impairment can start early in MS, with the survey showing that 45% of patients reported mobility issues within the first month after being diagnosed.

Early identification and management of mobility issues, including exercise and physical therapy, can help to improve quality of life for people with MS, Professor Belachew concluded. ♦

To list your event in this diary, email brief details to John Gustar at editorial@acnr.co.uk by 6th December, 2010

2010

November

Motivating the Unmotivated

1 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Management of Adult Central Nervous System Tumours

3 November, 2010; London, UK
www.bir.org.uk

Parkinson's Study day

3 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

International Symposium on Nitric Oxide-Cyclic Signal Transduction in Brain

4-6 November, 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

Clinical Reasoning in Soft Tissue Repair:

Using the evidence to maximise recovery using manual therapy, exercise and electrotherapy
6 November, 2010; Edinburgh, Scotland
www.physiouk.co.uk

MS Trust Annual Conference 2010

7-9 November, 2010; Kenilworth, UK
T. 01462 476700
F. 01462 476710
E. info@mstrust.org.uk

Posture & Balance in Neurological Conditions – Upper Limb Assistant

10 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

OZC – Communication, Assessment and Rehabilitation

11 November, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

UKABIF Annual Conference

11 November, 2010; London, UK
T. 01752 601318
E. ukabif@btconnect.com

An Introduction to Bobath Concept (Module 3)

11-12 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

How to do Cognitive Rehabilitation

13 November, 2010; Gatwick Airport, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

Clinical update of sleep disorder and the brain

15 November, 2010; London, UK
T. 020 7290 2984
E. sleep.disorders@rsm.ac.uk
www.rsm.ac.uk/academ/slb01.php
www.rsm.ac.uk/sleep

NanoBioTech-Montreux 2010

15-17 November, 2010; Montreux, Switzerland
www.nanotech-montreux.com

The West of England Seminars in Advanced Neurology (WESAN)

18-19 November, 2010; Exeter, UK
E. cgardnerthorpe@doctors.org.uk

3rd International Conference on Fixed Combination in the Treatment of Hypertension, Dyslipidemia and Diabetes Mellitus

18-20 November, 2010; Brisbane, Australia
T. +41 (0)22 5330 948
F. +41 (0)22 5802 953
E. fixed2010@fixedcombination.com

1st Rio International Eating Disorders and Obesity Conference

19-20 November, 2010; Rio de Janeiro, Brazil
E. anne.haylock@markallengroup.com

Electrotherapy Update: Current Concepts in Electrical Stimulation (Study Day 1)
20 November, 2010; Farnborough, UK
www.physiouk.co.uk

Electrotherapy Update: Current Concepts in Tissue Repair (Study Day 2)
21 November, 2010; Farnborough, UK
www.physiouk.co.uk

Cervical Auscultation
23 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Motivational Interviewing
25 November, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

Evolving MS Services
26 November, 2010; Liverpool, UK
T. 0208 438 0809
E. pcrossman@mssociety.org.uk

Parkinson's Disease Consultants Masterclass
24-26 November, 2010; Bristol/Bath, UK
T. 01872 225552
E. info@redpublish.co.uk
www.redpublish.co.uk/courses

6th Essential Neuro MRI Course
27 November, 2010; Liverpool, UK
T. 0151 5295416/5552
E. essentialneuromri@hotmail.co.uk

SpR Forum: Neurology
28-29 November, 2010; Manchester, UK
T. 01202 201223

Encephalitis Professional Seminar: Some Solutions and Emerging Changes
29 November, 2010; London, UK
T. 01635 692583
E. alina@encephalitis.info
www.encephalitis.info/Community/NewsEvants/Events.aspx

Posture & Balance in Neurological Conditions – Upper Limb, Qualified
29 November, 2010
T. 01332 254679
www.ncore.org.uk

The Birmingham Neurosurgery Meeting
30 November – 1 December 2010; Birmingham, UK
T. 0114 225 9057
E. academia.bbmuk@bbraun.com
www.aesculap-academia.co.uk

5th UK Stroke Forum Conference
30 November – 2 December 2010; Glasgow, Scotland
E. sally.atkinson@stroke.org.uk
www.ukstrokeforum.org

December

Anatomy & Mobilisation of Hands & Feet for Assistants
1 December, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

University Classes in Multiple Sclerosis VII
1 December, 2010; Fiuggi, Italy
E. m.friedrichs@charcot-ms.edu
www.charcot-ms.edu

Practitioner on Trial
2 December, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

The maternal embryonic interface
2-3 December, 2010; Valencia, Spain
E. catedrasg@cac.es
www.fundacioncac.es/catedrasg

European Charcot Foundation Lecture
2-4 December, 2010; Fiuggi, Italy
E. m.friedrichs@charcot-ms.edu
www.charcot-ms.edu

OZC – Understanding Brain Injury
3 December, 2010; Ely, UK
T. 01353 652173
E. Rachel.everett@ozc.nhs.uk

MA Healthcare 8th Bipolar Disorder Conference
3 December, 2010; London, UK
T. 020 7501 6762
www.mahealthcareevents.co.uk

Attention & Information Processing: Advanced Cognitive Rehabilitation Workshop
3-4 December, 2010; Gatwick Airport, London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

3rd National Sleep Disorders Conference
7 December, 2010; London, UK
E. anne.haylock@markallengroup.com

Kinetic Control: Theory & Concepts
7-8 December, 2010; Derby, UK
T. 01332 254679
www.ncore.org.uk

British Institute of Radiology: Imaging in Stroke – Update
8 December, 2010; London, UK
E. British_Institute_of_Radiology@mail.resp.com

The 7th International Congress on Mental Dysfunctions & Other Non-Motor features in Parkinson's Disease (MDPD 2010)
9-12 December, 2010; Barcelona, Spain
T. 41 229 080 488, F. 41 229 069 140
E. msaragosti@kenes.com
www.kenes.com

Biochemical Society Conference: Models of dementia
16-17 December, 2010; Cambridge, UK
E. elizabeth.faircliff@biochemistry.org
www.biochemistry.org/MeetingNo/SA120/view/Conference

2011

January

Cognitive Rehabilitation Workshop
14-15 January, 2011; Gatwick Airport, London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

British Paediatric Neurology Association Conference
26-28 January, 2011; Bolton, UK
T. 01204 492888
E. info@bpna.org.uk

Specialist Rehabilitation Course
27-28 January, 2011; Derby, UK
T. 01332 724735
E. Amy.Harte@nottingham.ac.uk

How to do Cognitive Rehabilitation
29 January, 2011; Gatwick Airport, London, UK
E. enquiries@braintretraining.co.uk
www.braintretraining.co.uk

February

Electrotherapy Update: Current Concepts in Electrical Stimulation (Study Day 1)
5 February, 2011; Elstree, UK
www.physiouk.co.uk

Electrotherapy Update: Current Concepts in Tissue Repair (Study Day 2)
6 February, 2011; Elstree, UK
www.physiouk.co.uk

112th Meeting of the British Neuropathological Society

January 5-7th 2011
Institute of Child Health, Guilford Street,
London WC1N 1EH

Symposium: "New Perspectives in Multiple Sclerosis"

Organiser: Professor Kenneth Smith, London, UK

Speakers: Professor Richard Reynolds, London, UK

Dr Klaus Schmierer, London, UK

Dr Don Mahad, Newcastle, UK

Professor Kenneth Smith, London, UK

Professor Robin Franklin, Cambridge, UK

Alfred Meyer Memorial Lecture: Professor Hans Lassmann, Brain Research Institute, Vienna, Austria

- Full programme of talks and posters
- The Society Dinner to be held at The Worshipful Company of Butchers, Butchers' Hall



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/>

http://www.ich.ucl.ac.uk/education/short_courses/courses/2T_79

World Parkinson Congress

Conference details: 28 September-1 October, 2010; Glasgow, UK. **Reviewed by:** Patrick Lewis, UCL Institute of Neurology.

The second World Parkinson Congress took place at the Scottish Exhibition and Conference Centre in Glasgow from the 28 September to 1 October, in a venue made famous by the likeness of its main hall to a metal armadillo. The World Parkinson Congress brings together several thousand researchers, clinicians, care givers and patients, providing a distinct forum where all the people studying and impacted by Parkinson's can exchange experiences, ideas and the latest research. This is by no means an easy task, as the different constituencies have very different expectations of a conference such as this but, having attended both of the Congresses held to date (the last one was in Washington DC in 2006), I have been impressed by how well the WPC achieves this.

The Congress, co-chaired by Andrew Lees (UCL Institute of Neurology, London UK) and Stanley Fahn (Columbia University, New York USA) opened, on the Tuesday, with a plenary session that emphasised the range of participants at the meeting. This included an introduction by Gavin Hastings, former captain of the Scottish and British Lions rugby teams, during which he gave a touching description of his wife developing and living with Parkinson's.

On to the conference itself and, as is clear following a cursory glance at the academic literature over the last 12 months, we live in exciting times with regard to research into the genetic and cellular basis of Parkinson's, with major advances occurring, most notably in the genetic definition of this disorder. This was underlined by a presentation from Haydeh Payami (Wadsworth Center, New York USA) following on from her recent *Nature Genetics* paper (Hamza et alia) describing a genome wide association study for idiopathic Parkinson's disease. Her team are interrogating the data generated for this study, and claim to have discovered a possible gene locus for the protective impact of caffeine in some Parkinson's patients. Although this was very much a preliminary report, and much more work is needed to confirm the finding, it offered an intriguing glimpse of what pharmacogenetics can offer.

A highlight of the first morning was a superb presentation by David Iverson, a journalist from San Francisco who has been diagnosed with Parkinson's, and whose father and brother both developed the disease. He has made a documentary about his experiences of Parkinson's which is available on the PBS website (<http://www.pbs.org/wgbh/pages/frontline/parkinsons/>), and I would encourage readers to visit this. It was particularly interesting to hear how someone deals with the probability that he or she has an inherited form of the disease, and the decisions that they face in terms of



whether or not to try and identify what is causing the disease in their family.

Continuing the genetics theme, there were some fascinating talks on altered rates of cancer in patients with mutations in LRRK2, the most common genetic cause of Parkinson's disease. Susan Bressman at the Beth Israel Medical Center in New York and Rivka Inzelberg of the Meir Hospital in Haifa both presented data showing that the common G2019S mutation of LRRK2 is linked to an increased rate in cancer (the New York study, by Saunders-Pullman and co-workers, has just been published). The balancing act between cell death, manifesting as neurodegeneration, and cell proliferation, manifesting as cancer, and their links to monogenic forms of disease is one that is of increasing interest to cell biologists researching PD, and this will only encourage them to redouble their efforts.

Another hot topic that was the subject of several talks in Glasgow was the possibility that alpha synuclein pathology in Parkinson's may be spreading via a prion-like mechanism. Research into this exploded following the description of Lewy body pathology spreading into fetal grafts implanted into the brains of patients (see the review by Brundin et alia for details), with a number of researchers using cell and animal models to try to dissect the mechanism of propagation. Again, this is an aspect of Parkinson's that we are only just beginning to understand, but it is encouraging to see some really outstanding work in progress.

Stem cells, and their potential to be used as replacement therapy for human disease, are an emotive subject for patients, for clinicians, for researchers and for society. There were several very impressive reports, on the clinical use of foetal transplants, the future use of stem cells in Parkinson's and on the basic biology of stem cells. Patrick Brundin from the University of Lund, Sweden, gave a comprehensive report on where transplants stand as a clinical treatment

now, highlighting their benefits and some of the pitfalls that have been encountered. Ole Isaacson (Harvard University, Boston USA) and Lorenz Studer (Sloan-Kettering Memorial Centre, New York USA) gave a pair of inspirational presentations on stem biology, describing the derivation of dopaminergic neurons for replacement and for modeling the disease process in cell culture (see Kriks and Studer, 2009 for a review of this). These were particularly timely presentations as the FDA have just licensed the first stem cell trial in humans, to be carried out on spinal cord injury patients (see <http://www.bbc.co.uk/news/health-11517680>), and it is only a matter of time before similar approaches are applied to neurodegenerative diseases such as Parkinson's.

In addition to all the research and patient news, there was a strong presence from the leading charities involved in funding research into Parkinson's and patient support groups. Parkinson's UK, The Michael J. Fox Foundation, and the Cure Parkinson's Trust all had very good and informative stalls. As for the research, the Congress provided a very useful forum for discovering where the charities are focusing their efforts and what funding mechanisms are available.

In summary, I found the Congress both enlightening and satisfyingly different from the majority of conferences on Parkinson's. From the point of view of basic researcher, the interaction between the patients, the clinicians and researchers is both a valuable and humbling experience, bringing into clear focus the human faces of the disease you are researching and I am looking forward to the next Congress, to be held in Quebec, Canada, in 2013. ♦

Acknowledgements

The author would like to thank Julia Fitzgerald for critical comments.

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References

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 - Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, Kusel VI, Collura R, Roberts J, Griffith A, Samii A, Scott WK, Nutt J, Factor SA, Payami H. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat Genet.* 2010 Sep;42(9):781-5
 - Kriks S, Studer L. Protocols for generating ES cell-derived dopamine neurons. *Adv Exp Med Biol.* 2009;651:101-11
 - Saunders-Pullman R, Barrett MJ, Stanley KM, Luciano MS, Shanker V, Severt L, Hunt A, Raymond D, Ozelius LJ, Bressman SB. LRRK2 G2019S mutations are associated with an increased cancer risk in Parkinson disease. *Mov Disord.* 2010 Sep 3. [Epub ahead of print]
- Image – Clyde Auditorium, freely available image from Wikipedia

20th Congress of the European Neurological Society

Conference details: 19-23 June, 2010; Berlin, Germany.

It was towards the end of June, when summer finally arrived in Central Europe too and the European Neurological Society gathered for their 20th anniversary meeting in Berlin, Germany. More than 3000 participants attended the meeting which again not only offered lectures held by the best experts in their respective fields of neurology during official symposia, but also high-quality education in the form of teaching courses, workshops and practical sessions. From the nearly 900 abstracts submitted, 125 were selected for an oral presentation. As in the past, the posters exhibited were highlighted by the popular poster walks, with an expert leading the discussion.

The topics treated during the meeting encompassed all fields in the neurological science and ranged from scientific research to clinical treatments. How rich the presented content was, is shown by the following summary.

Pathogenesis

Micro(mi)RNAs involved in the differentiation and regulation of CD4+ cells have been shown to play a role in relapsing remitting multiple sclerosis (RRMS); this might contribute to finding new therapeutic targets. On the contrary, the search for genetic risk factors involved in the susceptibility to progressive course of MS remains inconclusive. Nevertheless, novel targets have been identified, such as the HLA class II region, and represent potential candidates for further studies.

Calcitonin gene-related peptide (CGRP), which is a key molecule in the pathogenesis of migraine, has been shown to trigger migraine-like attacks in migraine patients with and without aura.

Gelatinase matrix metalloproteinases (MMP)-2 and 9 provide a link between neuronal degeneration and skin alteration in patients with amyotrophic lateral sclerosis (ALS). Another study showed a mitochondrial impairment in skin fibroblasts of patients with ALS, which is likely related to oxidative stress. These findings suggest that the skin abnormal-



ities may be a biomarker for monitoring ALS in the context of neuroprotective treatment trials.

Clinical findings

In myoclonus-dystonia, the clinical spectrum of DYT11 mutations includes patients with a non classical phenotype (i.e., lower limb onset, generalized distribution, and absence of family history).

The clinical characteristics of 1241 ALS patients included in an Italian prospective epidemiological register have been presented. Pyramidal and flail arm phenotypes had the better prognosis, while bulbar and respiratory phenotypes had the worst one. A smaller study showed that a more rapid progression was associated with a later onset of symptoms in patients with primary lateral sclerosis (PLS).

Compared with patients with Alzheimer's disease (AD), patients with frontotemporal lobar degeneration (FTLD) are characterised by a faster cognitive decline, which is independently associated with the language subtype and an early memory impairment.

In FTLD patients carrying exon 8 delCACT mutation of Progranulin (GRN) gene, cerebrospinal fluid (CSF) levels of total tau protein, phosphorylated-tau, and β -amyloid 1-42 were normal. This suggests that normal CSF biomarker may be consistent with a diagnosis of FTLD caused by GRN mutations.

Neuroimaging

The assessment of the regional distribution of damage to the normal-appearing white matter (NAWM) and gray matter (GM), using quantitative magnetic resonance (MR) techniques, may contribute to a phenotypic characterization of different neurological diseases, including MS, migraine, Leber's hereditary optic neuropathy (LHON), Parkinson's disease and atypical parkinsonisms, Alzheimer's disease (AD) and other dementias. Furthermore, it may improve the understanding of specific disease-related symptoms, such as fatigue in MS. The study of WM damage in AD patients also contributed to the understanding of atypical forms of early onset AD, such as posterior cortical atrophy and logopenic/phonological progressive aphasia.

MR imaging studies have identified objective markers of long-term clinical worsening in patients with different neurological conditions, such as thalamic damage in patients with MS and corticospinal tract damage in those with ALS.

ALS patients with mild disability have been shown to experience a dysfunction of resting state (RS) connectivity of the sensorimotor network. RS fMRI revealed also abnormalities of the visual network in LHON patients, which were correlated with structural damage along the visual pathways and disease duration.



Treatment

A substantial proportion of relapsing/remitting multiple sclerosis (RRMS) patients treated with cladribine were free from clinical and radiological disease activity over a short-course treatment (96 weeks). Fingolimod significantly reduced the annualized relapse rate compared with placebo regardless of prior disease-modifying therapies. In these patients, interferon β -1b affected the development of permanent black holes, which is a marker of permanent tissue destruction, at year 2 from active lesions at year 1, to a similar or better extent than glatiramer acetate. Data from the "TYSABRI observational program" showed that MS patients under natalizumab exhibit a very low level of

disease activity and the safety profile is consistent with that from the preregistration trials.

In patients with atrial fibrillation who have already suffered from a stroke or TIA, dabigatran 110 mg was as effective as warfarin, while dabigatran 150 mg bid was superior to warfarin. Both dosages of dabigatran also resulted in a relatively low rate of cerebral haemorrhages.

Bevacizumab in combination with fotemustine is a promising treatment for recurrent high grade gliomas with acceptable toxicity.

Apart from this excellent opportunity for education in cutting-edge neurological science and exchange of knowledge and experiences, the meeting's various social events also offered the possibility for more personal conversations and for meeting colleagues in a relaxed atmos-

phere. The dinosaurs in the Museum of Natural History watched as leading neurologists from all over the world mingled with residents and students at the occasion of the Welcome Reception. The banquet in the famous TIPI Tent offered the right ambience for the last evening of this meeting, which ended the next day again with high-quality workshops, teaching courses and two highlight symposia treating hot topics in neurology. ♦

*Prof. Massimo Filippi,
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7th FENS Forum of European Neuroscience

Conference details: 3-7 July, 2010; Amsterdam, The Netherlands. *Reviewed by:* Bauke M. de Jong, MD, PhD.

On Saturday July 3rd, neuroscientists from all over Europe, as well as colleagues from more distant continents, gathered in the RAI Congress Centre in Amsterdam to participate in the openings ceremony of the FENS Forum 2010, the 7th biannual conference of the Federation of European Neuroscience Societies. Attendees thus started to familiarise both with each other and the conference venue. The latter was characterised by a spacy atmosphere, not in the least due to an excellent ordering of poster boards surrounding the exhibition area with a large central meeting point. Weather was fine and rented bikes were widely used, next to public transportation. The oral forum presentations comprised 9 plenary sessions, 10 special lectures and 7 blocks of 8 parallel 90 min symposia with 4 speakers each. Seven workshops were given before the opening. Themes reflected the wide scope of topics at molecular, cellular, neuronal network and behavioural levels, aimed at understanding both normal brain function and brains affected by disease. In this respect, the symposium was of interest for basic neuroscientists as well as neurological and psychiatric disciplines.

In particular the synergy of the four presentations in the symposia provided an excellent forum for enhancing synergy and generating novel points of view. As a symposium organiser, I personally experienced such positive interaction between contributing speakers in the symposium 'Prefrontal and parietal-premotor contributions to free choice selection'. Our symposium illustrated research on a fundamental level, providing a balanced perspective on a hierarchy in action selection, reaching from response freedom of single neurons at early sensorimotor processing stages to action selection experienced as the result of free will. Sensing a free will is closely



related to the feeling of ownership of one's body. In the symposium of Henrik Ehrsson on this topic, the illusion of feeling an observed rubber hand provided a starting point for future perspectives on practical applications to enhance the sense of prosthetic limbs as being a 'real' part of one's own body.

The fMRI work of Maurizio Corbetta in stroke patients can also be placed at the interfaces of basic neuroscience, clinical neurology and rehabilitation. Identifying sites of interaction between separate resting state networks involved in attention and controlling arm movement, respectively, distant from the lesion location, helped to predict recovery and functional outcome. Such new brain scan technology may thus offer new approaches in treatment and targeted strategies for rehabilitation. With regard to molecular aspects of stroke treatment, Denis Vivien presented results from animal experiments demonstrating that immunotherapy with antibodies might prevent secondary brain damage following stroke, including side-effects of acute thrombolysis.

Advances at molecular level of neuronal functioning were addressed in plenary lectures concerning, for example, the role of adhesion molecules in synaptic plasticity and regeneration (Melitta Schachner), and tau pathology in neurodegenerative disorders (Maria Spillantini). In a symposium on microRNAs, new data on their role in fine-tuning synaptic development and the consequence of deregulation for the emergence of neurodegeneration in Alzheimer's and Parkinson's disease were addressed.

Clearly, given the quality of presented research, an increasing number of neuroscientists from outside Europe can also be expected to attend future FENS conferences. <http://forum.fens.org/2010>. ♦

Merck Serono to Appeal CHMP Opinion on Cladribine Tablets in MS

Merck Serono has notified the European Medicines Agency (EMA) of its intention to request a re-examination of the opinion issued by the Committee for Medicinal Products for Human Use (CHMP) in September regarding Cladribine Tablets as a treatment for relapsing-remitting multiple sclerosis (MS).

"We are committed to the potential of Cladribine Tablets to meet an unmet medical need and to make this treatment option available to patients who could benefit from it," said Elmar Schnee, President of Merck Serono. "We will continue working closely with the CHMP to address the committee's concerns and pursue a way forward."

In accordance with European regulations, applicants may appeal a CHMP opinion provided they notify the EMA in writing of their intention to appeal within 15 days of receipt of the opinion. The applicant must provide to the agency with detailed

grounds for a re-examination of the opinion within 60 days after receipt of the opinion.

Cladribine Approved in Australia

On 3rd September, The Australian Therapeutic Goods Administration (TGA) approved Cladribine Tablets for the treatment of relapsing-remitting multiple sclerosis. Cladribine Tablets will be registered in Australia under the trade name Movectro®.

Cladribine Tablets, also under the trade name Movectro, became the first oral MS treatment in the world to gain marketing authorisation when health authorities in Russia approved it in July 2010.

For further information contact Merck Serono on E. medinfo.uk@merckserono.net or T. +44 (0)20 8818 7373.

Milestone Ruling for Alzheimer's Disease Patients Announced

The National Institute for Health and Clinical Excellence (NICE) has announced new draft guidance which represents a significant step towards ensuring patients with Alzheimer's disease in England and Wales receive treatment for their condition, from the early stages of disease.

New draft NICE guidance recommends that acetylcholinesterase inhibitors, including Aricept® (donepezil), should be made available to patients in England and Wales as options for managing mild to moderate disease. This is a significant change to an earlier 2006 NICE ruling which restricted access to these medicines for patients with moderate disease only.

"This provisional decision by NICE is an important milestone for the thousands of Alzheimer's patients currently unable to receive treatment for their condition. Early diagnosis and access to medication is critical to help reduce both the short and long-term impact of this devastating condition on patients, families and carers," says Professor Roy Jones from The Research Institute for the Care of Older People (RICE) Centre, Royal United Hospital, Bath, UK.

The announcement supports the Department of Health's National Dementia Strategy (NDS). The NDS encourages the active management of Alzheimer's disease from its earlier stages to minimise the burden of the condition on patients, their carers and society. In addition, the need for greater access to dementia-specific treatments is in line with the recent Alzheimer's Disease International report which calls for governments to make dementia a higher health priority, to help tackle the huge burden of the disease. The draft NICE recommendations on Alzheimer's disease treatment will now go into consultation, with final guidance expected in early 2011.

For the full guidance, see <http://guidance.nice.org.uk/Type/TA/Published>

Government Listens to Epilepsy Campaigners

The government has decided not to make generic prescription of NHS drugs compulsory.

Supporters of The National Society for Epilepsy's (NSE's) 'Count Epilepsy Out' campaign sent campaign postcards and letters, earlier this year, to the Minister of State for Health saying that cutting costs on epilepsy drugs doesn't add up. It could provoke seizures or side effects – with a high cost to both the NHS and the person with epilepsy. The NSE also submitted an in-depth response to the consultation laying out the potential dangers of generic substitution to people with epilepsy. This backed up an earlier report that was formative in the government's decision to consult on their plan.

This campaign contributed to the government's rejection of the scheme. In the Department of Health press release Health Minister Lord Howe says, "We have listened to the concerns from the public, patients and other interested parties... It is

not clear whether the proposals would have provided a substantial benefit to the NHS."

People with epilepsy have been nervous about the long wait since the Department of Health's consultation closed in March 2010. Breakthrough seizures can be caused if their drug is swapped for non-clinical reasons. One breakthrough seizure is devastating and could cause serious injury and harm, rob someone of their driving licence and affect their job.

"Thank you to all our supporters who sent a postcard and wrote to the Minister of State," said NSE chief executive Graham Faulkner. "Working together we have made a big contribution to a great result for people with epilepsy. This does show that we can make a difference."

For the full guidance, see <http://guidance.nice.org.uk/Type/TA/Published>

Advancing Scientific Understanding of Autism

The Wales Autism Research Centre at the School of Psychology, Cardiff University, has been established with support from the charities Autism Cymru and Autistica, and from the Welsh Assembly Government.

Autism affects up to one child in every 100. Those affected have difficulties in communicating, forming relationships and making sense of the world. The new Centre will research new areas in identification, diagnosis, development and intervention.

Director of the Centre, Professor Susan Leekam said, "The launch of the Wales Autism Research Centre marks the beginning of an exceptional opportunity to advance scientific research. We will not only be carrying out internationally competitive research projects but also helping to build evidence-based policy and

practice. This mission is supported by partnerships between scientists, practitioners and government policy makers, and makes the purpose of this research centre unique in the UK."

The Centre already has a number of new projects underway. These include research on sensory processing using neuroimaging techniques, research on clinical symptoms and diagnostic tools and research on the effects of interventions. The team has also been contributing to a schools training programme, evaluating diagnosis services, assisting with awareness-raising materials and investigating the potential for new databases of information.

Researchers at the Centre have also set up new collaborations and networks with the University's pioneering Cardiff University Brain

Research Imaging Centre (CUBRIC) and Cardiff Neurosciences Centre.

The Welsh Assembly Government's Strategic Action Plan for Autism Spectrum Disorder is believed to be the first of its kind anywhere in the world. Uniquely, the Centre works with practitioners and government policy makers within this action plan to integrate research evidence with policy and practice. It also aims to raise public and professional awareness of autism research, highlighting the importance of reliable, scientific evidence and breaking down some of the myths surrounding it.

For more information T. 02920 879074



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PRE-FILLED SYRINGE PRESCRIBING INFORMATION

Presentation – Glatiramer acetate 20mg solution for injection in 1ml Pre-filled Syringe. **Indication** – Treatment of patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (MS). Reduction of frequency of relapses in relapsing-remitting MS in ambulatory patients. In clinical trials this was characterised by at least two attacks of neurological dysfunction over the preceding two-year period. **Dosage and administration** – 20mg of glatiramer acetate (one pre-filled syringe) administered sub-cutaneously once daily. **Children (12 - 18 years)** No specific studies. Limited published data suggest the safety profile of 20mg administered sub-cutaneously once daily is similar to that seen in adults. **Children (<12 years)** Not recommended. **Elderly** No specific data. **Impaired renal function** No specific studies. Monitor renal function during treatment and consider possibility of deposition of immune complexes. **Contra-indications** – Known allergy to glatiramer acetate or mannitol (excipient). **Pregnancy. Special warnings and precautions** – Sub-cutaneous use only. Initiation to be supervised by neurologist or experienced physician. Supervise first self-injection and for 30 minutes after. One or more of vasodilatation, chest pain, dyspnoea, palpitations or tachycardia may occur within minutes after injection. These generally resolve spontaneously after a short time. If severe, treat symptomatically. Caution in patients with pre-existing cardiac disorders and review such patients regularly. Rarely convulsions and/or anaphylactic or

allergic reactions. Rarely, hypersensitivity (bronchospasm, anaphylaxis or urticaria). If severe, treat appropriately and discontinue Copaxone. **Interactions** – No formal evaluation. Increased incidence of injection-site reactions with concurrent corticosteroids. Theoretical potential to affect distribution of protein-bound drugs, therefore concomitant use of these should be monitored. **Pregnancy and lactation** – Not to be used in pregnancy. Consider contraceptive cover. No data on excretion in human milk. **Undesirable effects** – Local injection site reactions (erythema, pain, mass, pruritus, oedema, inflammation, hypersensitivity, injection site atrophy). An immediate post-injection reaction (one or more of vasodilation, chest pain, dyspnoea, palpitation, tachycardia) may occur within minutes, reported at least once by 31% of patients receiving Copaxone compared to 13% of patients receiving placebo. Other undesirable effects more than 2% (>2/100) higher incidence in the Copaxone treatment group than in the placebo group: Nausea, anxiety, rash, back pain, chills, face oedema, vomiting, skin disorder, lymphadenopathy, tremor, eye disorder, vaginal candidiasis, weight increased. Rarely: Anaphylactoid reactions. Please refer to the SPC for a full list of adverse effects. **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. Do not freeze. **Legal Category** – POM. **Package Quantity and Basic NHS Cost** – 28 pre-filled syringes of Copaxone: £513.95. **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** – December 2009.

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.

Date of Preparation: May 2010

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