

EDITOR'S CHOICE

MULTIPLE SCLEROSIS: controversial benefit of the interferons

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

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

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

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

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

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

needed to treat with interferon early, rather than late, to avoid one person acquiring fixed disability over three years is 12.

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

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

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

1. ABN Guidelines for Treatment of Multiple Sclerosis with beta-interferon and Glatiramer Acetate 2007. <http://www.theabn.org/downloads/ABN-MS-Guidelines-2007.pdf>
2. Scolding N, Wilkins A, Cottrell D. *New Guidelines for MS Treatment - no cause for celebration*. *ACNR* 2007;7(3):17-18.
3. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownschidle CM, Murray TJ, Simonian NA, Slator PJ, Sandrock AW. *Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis*. CHAMPS Study Group. *N Engl J Med* 2000;343:898-904.
4. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, Hartung H, Seeltrayers P, Sorensen PS, Rovaris M, Martinelli V, Hommes OR. *Early Treatment of Multiple Sclerosis Study Group. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study*. *Lancet* 2001;357:1576-82.
5. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jacobs P, Pohl C, Sandbrink R. *Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes*. *Neurology* 2006;67:1242-49.

Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Radu EW, Bauer L, Dahms S, Lanius V, Pohl C, Sandbrink R; BENEFIT Study Group.

Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study.

LANCET

2007 Aug 4;370(9585):389-97.

HEADACHE: Valproate for chronic headache

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

Freitag FG, Diamond S, Diamond ML, Urban GJ.

Divalproex in the long term treatment of chronic daily headache.

HEADACHE

2007;41:271-8.

PARKINSON'S DISEASE: Pacemakers and pathogenesis

*** RECOMMENDED

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

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

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

Chan CS, Guzman JN, Iljic E, Mercer JN, Rick C, Tkatch T, Meredith GE, Surmeier DJ.

Rejuvenation' protects neurons in mouse models of Parkinson's disease.

NATURE

2007; 447:1081-1087.

Lindholm P, Voutilainen MH, Lauren J, Peranen J, Leppanen VM, Andressoo JO, Lindahl M, Janhunen S, Kalkkinen N, Timmusk T, Tuominen RK, Saarma M.

Novel neurotrophic factor CDNF protects and rescues midbrain dopamine neurons in vivo.

NATURE

2007; 448:73-78.

BRAIN INJURY: and mobile phones

*** RECOMMENDED

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

Stapleton S, Adams M, Atterton L.

A mobile phone as a memory aid for individuals with traumatic brain injury: a preliminary investigation.

BRAIN INJURY

2007; 21(4):401-11.

HUNTINGTON'S DISEASE: and disgust

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

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

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

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

BRAIN

2007;130:1732-44.

HEADACHE: Mechanisms of trigeminal ganglion signalling

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

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

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

HEADACHE

2007;47:1008-23.

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

*** RECOMMENDED

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

Manikandan N.

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

CLINICAL REHABILITATION

2007;21:338-43.

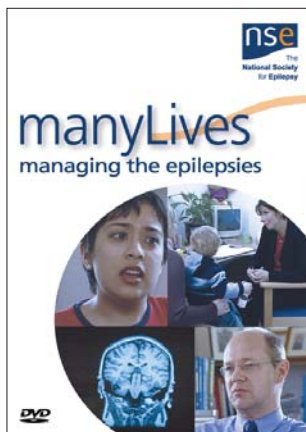
Journal reviewers

Heather Angus-Leppan, Royal Free & Barnet Hospitals;
Chrystalina Antoniadou, Cambridge Centre for Brain Repair;
Roger Barker, Cambridge Centre for Brain Repair;
Lloyd Bradley, Colman Centre for Specialist Neurological
Rehabilitation Services in Norwich;

Alasdair Coles, Cambridge University;
Andrew Larner, Walton Centre, Liverpool;
Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospitals;
Wendy Phillips, Addenbrooke's Hospital, Cambridge;
Robert Redfern, Morriston Hospital, Swansea;
Ailie Turton, University of Bristol.

News Review

Latest thinking on treating epilepsy at special price



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

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

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

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

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