

The meeting of the American Academy of Neurology

Conference details: 25 April-2 May, 2009; Seattle, USA. *Reviewed by:* Alasdair Coles, Cambridge, UK.

A tale of four treatments

Time was when neurologists were accused of being interested only in diagnosis and not treatment. At best we might disdainfully prescribe steroids, but usually we were content to watch the natural history of the disorder we had so cleverly delineated. That stereotype has been whittled away by anticonvulsants and stroke treatments, of course. But never before have I felt so resoundingly among therapists, rather than diagnosticians, than at this year's AAN. Four treatments caught my attention particularly.

Rapamycin and tuberose sclerosis

David Franz, of the University of Cincinnati, presented breath-taking data to show that tuberose sclerosis, that nasty genetic disorder causing astrocytomas, seizures, developmental delay, behavioural problems and skin abnormalities, may be treatable! This story has emerged from understanding the molecular pathogenesis of TS. The two causative genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin respectively, both normally act to inhibit mTOR. mTOR is a "master switch" of protein synthesis and is highly conserved across species. In TS, mTOR is released to become overactive. Happily, mTOR is also the target of rapamycin and its derivatives, so the obvious question is: can inhibition of mTOR compensate for the lack of hamartin or tuberin in TS? Franz's group had previously shown that it does: in 2006 reporting that it shrinks astrocytomas in TS. Now he reported on a trial of RAD001, a variant of rapamycin, in

28 patients. On MRI, the size of the subependymal nodules reduced. And MRI spectroscopy suggested that the astrocytomas in these patients seemed to change towards a chemical profile more like subependymal nodules. Clinically, patients' EEGs and seizures vastly improved. And there was even evidence of a reversal of cognitive impairment.

Deep brain stimulation and depression

Helen Mayberg, from Emory University, Atlanta, Georgia, is a neurologist who has stepped over the abyss to psychiatry and taken with her functional imaging and DBS. She has been championing DBS for depression for some years. Her thinking arose from the demonstration –through functional imaging– of overactivity of the subcallosal cingulate gyrus in depression; and that successful treatments of depression (drugs and ECT) reduce this overactivity. So she has performed two uncontrolled studies of DBS stimulation of the subcallosal cingulate gyrus in depression. In the larger, of 20 patients followed for one year, reported in *Biological Psychiatry*, she reports a 55% response. Given that these patients were regarded as treatment-resistant and chronically disabled, that seems pretty good to me. More rigorous trials are planned. What most struck me was her report of the effect of the treatment. It seems that DBS of the subcallosal cingulate gyrus specifically reduces the negative aspects of depression. And it does so very rapidly. As Mayberg has said in an interview: "In general, patients described a sudden disappearance of something negative, which was

more often than not a change in a visceral state: a sudden sense of intense calm and relief, clearing of mental heaviness, lifting of a black cloud, the disappearance of a void, fading of a burrowing dread in the pit of the stomach, are some examples. Of interest, the turning off of these negative sensations was followed almost immediately by a change in attention and interest with objective evidence of increased spontaneous speech and motor speed."

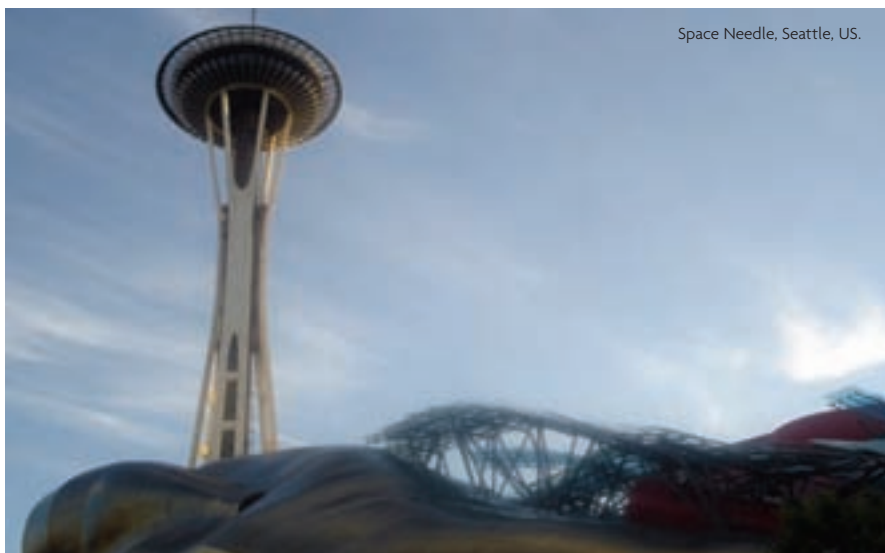
Pills to treat multiple sclerosis

The results of two phase 3 trials of oral treatments of multiple sclerosis were reported. Both trials were large, involving over one thousand people with relapsing-remitting multiple sclerosis, who had little disability, tested with two different doses of the new drug. We can expect to see both drugs emerging into the clinic in the next 2-3 years.

Gavin Giovannoni, from London, presented the final results of the CLARITY study of Cladribine (n=1326). Cladribine is taken in quite a unique way: 1 or 2 tablets for 4-5 days in the month, for 2 to 4 months in the year! In other words, a patient takes literally a handful of tablets a year. In this trial, it was compared with placebo over 96 weeks. Cladribine reduced the relapse rate by 55-58% and reduced the chance of getting disabled by roughly 31-33%. 2% got a reactivation of shingles and there were four cancers in those taking cladribine (n=884), with none in the placebo arm.

Jeff Cohen, from Cleveland, reported the final results of the TRANFORMS study of fingolomid (n=1292). Fingolomid (which is sometimes called FTY720) is taken as a pill once a day and was compared over one year with beta-interferon. Fingolomid was more efficacious at reducing the relapse rate (on fingolomid there were 40-50% fewer attacks) but –disappointingly– it did not reduce the rate at which people acquired fixed disability. There were some slightly worrying side-effects: there were two fatal viral infections (disseminated varicella zoster and herpes encephalitis), 1-2% incidence of cardiac AV block and 8 skin cancers (compared to 2 on interferon).

These new drugs potentially fit into the category of being convenient, reasonably effective with real, but low-level, side-effect concerns. It is likely that they will steal a sizeable share of the interferon market, leaving that drug for those with mild disease or people who want the almost risk-free interferons. ♦



Space Needle, Seattle, US.

Non-Motor Symptoms in Parkinson's Disease: What's New? Fourth Meeting of the UK PD Non Motor Group

Conference details: 21 March 2009, London, UK. **Reviewed by:** Kartik Logishetty and K Ray Chaudhuri, National Parkinson Foundation Centre of Excellence, King's College Hospital and University Hospital Lewisham, London, UK.

The fourth annual meeting of the UK Parkinson's Disease Non-Motor Group (PDNMG) was the largest yet, with over 200 delegates attending the Royal Society of Medicine, London. This in part reflects the continued and increased recognition of Parkinson's Disease (PD) as a non-motor disease as much as a motor one.

After a brief introduction by PDNMG Chairman and Meeting Organiser, Prof KR Chaudhuri (UK), all delegates attended lectures on Olfaction and Sleep in PD (Prof H Reichmann, Germany) and Imaging of NMS in PD (Prof D Brooks, UK).

Bilateral and invariable impaired olfaction is now a recognised early NMS, and occurs in 70-100% of all PD patients independent of medication. Earlier diagnosis based on olfactory symptoms, may be pivotal to treatment choice and prognosis.

Early idiopathic olfactory dysfunction has also been shown to coincide with abnormalities on parenchymal sonography of the substantia nigra (SN) and Beta-CIT SPECT imaging. People identified as suffering from olfactory dysfunction are five times as likely to subsequently develop PD within four years, compared to normosmic individuals. Olfaction may thus have utility as a screening tool to detect those at high risk of developing PD or 'preclinical' PD.

Although it appears that dopamine modulates executive function and sleep, there is no correlation between striatal dopamine and fatigue symptoms. Instead, decreased dopamine in the right insular and ventral thalamic connections are correlated with fatigue. Dementia is associated with decreased parietotemporal metabolism, as well as decreased frontal lobe dopamine storage and cortical cholinergic function. Although decreased serotonin is seen in PD with depression, Prof Brooks suggested that this symptom relates more to noradrenaline and limbic dopamine concentrations.

Cardiac MIBG scans, imaging the sympathetic nervous system, have shown a post-ganglionic deficiency in patients with PD. Recent evidence suggests that cardiac MIBG scans of patients with REM Sleep Behaviour Disorder (RBD) shows the same pattern of autonomic dysfunction, further substantiating RBD as a pre-motor NMS in PD. This is reflected by reduced uptake seen on DAT and PET imaging in RBD patients, in the same pattern as with patients with PD alone.

The next lectures, given by Prof P Jenner (UK) and Prof A Schapira (UK), looked at



non-dopaminergic therapies in PD, and the question of when to start treatment in PD, respectively.

Use of non-dopaminergic treatments to treat PD is widespread. The wide range of transmitters and brain areas altered in PD, in addition to nigrocentric, dopaminergic systems, emphasises the importance of taking a global approach to management. Prof Jenner pointed to the relative success of toxin-based models such as the 6-OHDA lesioned rat and the MPTP or treated primate for the introduction of new therapeutic strategies for the motor symptoms of PD. However, the development of treatment for NMS has been slow, e.g. Sarizotan (a 5HT_{1A}-agonist), and the effects of non-dopaminergic drugs in models do not translate into clinical efficacy. Perampanel, an AMPA-type glutamate receptor antagonist, has also failed in recent trials. Similarly, there has been little real

progress in treating NMS in PD as a group, with clinicians still having to address each symptom individually.

Prof Jenner outlined how none of the currently used models reproduce all the key features of pathogenesis specific to PD. Rather than waiting for models based on gene-gene/gene-toxin interactions in familial PD, he discussed methods to mimic Lewy Body formation including using injection of lipopolysaccharide into the SN to initiate inflammation, peroxynitrite formation and cytokine release, and using proteasomal inhibitors such as PSI and epoxymycin. However the ultimate goal is modifying disease progression and identifying 'at risk' populations to target with neuropreventative strategies.

'When' to treat is as perplexing a question as 'how'. Due to the heterogeneity of PD, pre-symptomatic time is variable, and clues to diagnosis, whether clinical, pathological, imaging-based or genetic, are crude estimates. The long 'pre-symptomatic' period, where there is evidence of dopaminergic and nigrostriatal cell degeneration without motor symptoms, must be exploited. To explain this, Professor Schapira supported a 'theory of compensation' – other parts of the brain compensate and therefore correct early basal ganglia dysfunction.

Treatment of PD appears to have short-term side effects and long-term complications. However, evidence based reappraisal appears to recommend early symptomatic relief and improved quality of life, despite the inevitable undesirable effects of treatment, such as wearing off. Treatment-naïve patients have lower quality-of-life scores than those receiving treatment, and early intervention should become common practice. More so, recent evidence from DATATOP, ELLDOPA, ADAGIO, and TEMPO studies even suggest better outcomes, perhaps due to a neuroprotective mechanism, for PD patients started on early treatment.

The morning's second session focused on the issue on sleepiness and parasomnias in PD. Excessive daytime sleepiness (EDS) is a frequent and disabling symptom of PD. It can result from lesions in arousal systems causing abnormal night time sleep, or as a side effect of dopaminergic treatment. Patients taking dopamine agonists are three times as likely to suffer from EDS than those on Levodopa alone. Dopamine related sleepiness occurs most often at the peak of dopamine serum concentration. However, there is only weak evidence that prolonged-release dopaminergic treatment is less sedative.

Dr I Arnulf (France) reviewed promising data on sodium oxybutyrate, an anti-narcoleptic. Small trials have shown significant decreases in Epworth Sleepiness Scale scores in patients with PD and EDS. Phase II studies have also recently shown histamine-3 receptor antagonists to reduce EDS and motor symptoms.

Prof C Trenkwalder (Germany) demonstrated the difficulty of diagnosing RBD. Although caregiver history is essential, objective evidence from polysomnography is the gold-standard device for confirming this parasomnia. RBD can change the motor-pattern during sleep, compared to daytime movements. It is also typical for vocalisation to be combined with motor acting, often in the extremities.

An individual with idiopathic RBD has a higher risk of developing Lewy Body Dementia (LBD) or PD. Prof Trenkwalder suggested that a flip-flop switch, which normally controls the onset of REM-Sleep, is dysregulated in PD. Lesions in the mesopontine tegmentum may be responsible.

Despite its debilitating effects on the quality of life of patient and carer, there is a deficiency of clinical trials looking at the treatment of RBD. Prof Trenkwalder echoed widespread recommendations of clonazepam or melatonin, and called for controlled trials comparing treatment strategies.

The final speaker of the session, Prof CJ Fowler (UK), discussed bladder dysfunction in PD. These problems are notoriously difficult to treat, and often associate with advanced PD. It is essential that any treatable urological cause of bladder dysfunction is first excluded. Prof Fowler stressed the importance of selecting anticholinergic drugs that do not affect central M1 receptors and do not cross the blood-brain barrier. Botulinum injection directly into the bladder wall is an exciting, albeit challenging, new treatment that can prevent hyper-reflexia, urgency and overactivity.

In a series of 'snapshot reviews' Prof Chaudhuri highlighted first the need for more research into visual dysfunction in PD. A range of visual problems may be seen in patients, ranging from retinal defects leading to contrast sensitivity or diminished blue-green colour vision, to motor defects presenting as diplopia, hypometria or dyskinesias. These NMS may be again part of a pre-motor complex, and may be best recognised using the Farnsworth-Munsell 100 Hue Test. There is a paucity of evidence that suggests that colour discrimination in PD patients is improved after ingesting levodopa.

Prof T Renton (UK) briefly evaluated trigeminal pain in PD. Pain appears to be both prodromal and prognostic. Oculofacial pain (OFF) is extremely debilitating, and is associated with headaches, burning mouth syndrome, temporomandibular joint pain, and compromised trigeminal reflexes. Research currently being conducted by Prof Renton hopes to better identify the aetiology of OFF in PD.

The afternoon's lectures took on a new format once more, with delegates splitting into

three symposia addressing therapy in advanced disease, psychiatric issues and dopamine agonists, and co-morbidities and quality of life in PD.

Duodopa can have a powerful effect on motor function, with patients seeing a 70%-90% reduction in off-time, and reduced dyskinesia. More so, unpublished data suggests that pump therapies reduce NMS by 55%, particularly improving perception, and alleviating urinary dysfunction and depression. This needs to be offset against device-related problems and cost.

Deep brain stimulation (DBS) also improves motor symptoms and quality of life, although its effects on NMS and neurocognitive side-effects are less well-defined.

Psychiatric issues, particularly depression and compulsive behaviour, dominated discussion in the second symposium. Regarding the treatment of depression in PD, tricyclic antidepressants (TCAs) may be more effective than SSRIs, whilst pramipexole has significant antidepressive properties. The third and final symposium reviewed new developments in determining comorbidities of PD and their effects on health-related quality of life (HRQoL). Trials

there is an increased stride-to-stride variability and decreased speed, in direct proportion to the difficulty of the cognitive challenge.

Similarly, predictive features of falls in PD patients are dopamine agonist treatment, power of attention, and reaction time variability. Freezing of gait (FoG) is related to emotional state and cognitive function. It was suggested then that a dysfunction in mobility – an unequivocally motor symptom – is perhaps a cognitive, and therefore non-motor, symptom too.

The second plenary, and the final discussion, of the meeting was led by Prof D Burn (UK). Dementia has now been identified as a common and core feature of PD, typified by insidious onset and slow progression. Patients suffer from cognitive dysfunction, neuropsychiatric burden, and fluctuating attention. Prof Burn reviewed the numerous tools available to assess cognition in PD, and concluded that the Mini Mental State Examination is not sensitive. The Addenbrooke's Cognitive Examination (ACE-R), the Montreal Cognitive Assessment, and the Neuropsychiatric Inventories (including NP4) were recommended as screening tools.

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currently underway may provide a solution to constipation using botulinum toxin. The importance of checking the mouth for signs of oral infection, to prevent aspiration pneumonia, was emphasised for patients with drooling and swallowing difficulties. Prof Martinez-Martin (Spain) reiterated the need for longitudinal studies on PD-HRQoL. Physicians should be acutely aware of the difference between symptoms that are determinants of HRQoL and those that dominate the clinical picture. The problems that are therefore most relevant to the patient can be identified, and the treatment pathway guided appropriately.

The first plenary speaker, Prof N Giladi (Israel), brought a fresh perspective to the Meeting. The recent National Parkinson's Foundation opinion meeting agreed that depression and anxiety, cognitive disturbances, and immobility and falls, are the most important features of PD from a patient's perspective. Prof Giladi was keen to note that just one of these is motor, further emphasising the redefinition of PD.

Volition, planning and cognitive inhibition define executive function in successful, normal gait. PD patients who must stop walking to talk exhibit a lack of cognitive reserve. When PD patients attempt to do both simultaneously,

Diagnostic criteria take classical clinical features into account, but require prospective validation to ascertain a gold-standard.

The variability in methods of diagnosing dementia in PD is equalled by the range of treatment approaches, all of which are sub-optimal. The results from the use of memantine in Lewy body dementia are awaited. Although supported only by a weak evidence base, quetiapine is currently the first choice atypical anti-psychotic therapy for the treatment of dementia in PD, although should only be used after all dopaminergic therapy options have been exhausted to treat symptoms.

The awarding of poster prizes and a brief vote of thanks by Prof Chaudhuri rounded off the day. The interpretation of symptoms and the description of Parkinson's disease is now in a state of flux. Queries remain about the clinical relevance of the pathophysiology, the definition of the disease as a motor and non-motor complex, and the potential neuroprotective effects of treatment, to name just three fragments of a growing puzzle. The pioneering research presented at the meeting was a testament to the exponential pace of research into PD. Fresh answers are generating new questions, and progress can only be made in an environment of translational medicine. ♦

International Society for Magnetic Resonance in Medicine (ISMRM) 17th Scientific Meeting and Exhibition

Conference details: 18-24 April, 2009; Honolulu, Hawaii. **Reviewed by:** Dr Waqar Rashid, Consultant Neurologist, Hurstwood Park Neurological Centre, Brighton, UK.

The 17th meeting of the International Society for Magnetic Resonance in medicine (ISMRM) again provided an excellent mix of cutting edge technological advance in imaging coupled with their application to all specialities of medicine. Stationed in the glamorous location of Honolulu, the North American organisers laid on a huge event with over 850 oral presentations, 2242 traditional posters and 1691 multimedia e-posters. It appears the organisers have (perhaps not surprisingly!) an affinity for this location as it was the second time the conference was held in Hawaii in seven years.

Preceding the main meeting itself were two days of educational courses which give a thorough rundown of the various imaging techniques starting (very usefully) at a basic level and becoming ever more complex. The meeting itself has a fine line to tread to maintain a balance in trying to provide enough clinically based presentations to keep the clinician happy, in addition to papers reporting, for example, how a minute echo time change coupled with a different gradient spoiler can help improve a new echo planar imaging sequence (very much more for the benefit of the physicists!). To a large degree this balancing act is achieved and there was much for a neurologist (not just one with an imaging research background like myself) to find of interest. It was also noticeable that there were a large number of presentations on a number of conditions in addition to the usual large body of work on multiple sclerosis (MS).

Now for the presentations I found of most interest. Well it is amazing how this technology is moving on, and faster and more refined magnetic resonance imaging (MRI) sequences are becoming a reality allowing increased brain coverage with greater resolution in shorter times. This increases measured signal and reduces artefact and with suitable adjustments to various parameters, tissue types can be differentially viewed to look for specific pathology. This was elegantly shown in a presentation by SCL Deoni describing a new sequence mcDESPOt (acronyms were very popular at the meeting!) which uses multiple relaxation times to allow measurement of tissue myelin fraction with obvious applications for assessing demyelination in MS.¹ Another interesting paper reinforced the importance in predicting progression of the location rather than the quantity of lesions in primary progressive MS.² The apparent disparity between lesion loads as viewed on MRI with a patient's

actual disability has long been a frustration for both neurologist and clinical trial designer alike. The suggestion here and from other previous publications³ is that although not all brain lesions are predictive of clinical state, some might be and therefore with appropriate modelling MRI may yet give useful information for patient prognostication.

There was a mixed bag of other MS based presentations. Certain popular themes however did emerge, with further imaging sequences and refinements used to try to visualise cortical lesions with greater degree of sensitivity and also a number of papers applying higher strength magnets to a number of known quantitative MR techniques to discern feasibility and potential further larger scale research use. The acquirement of a 7 tesla scanner in Nottingham spawned a number of presentations highlighting potential future interest.



View of Honolulu from on high
(Courtesy of www.visitingdc.com/airports/honolulu-airport-...)

There were also some excellent presentations on neurodegenerative disease and movement disorders also. A number of presentations looked at the application of tractography and functional MRI in these conditions, suggesting metabolic abnormalities in areas of the brain specific to these disorders. In addition, Zhang et al demonstrated different MR perfusion and diffusion characteristics of Alzheimer's disease and frontotemporal dementia, potentially aiding specificity of diagnosis of these disorders.⁴

The poster section contained a vast amount of information and selectivity was the order of each day to prevent an overload of information! It was interesting to note how widespread research is now in implementing imaging to study virtually any neurological disorder one can think of.

Another major part of the conference is the study group meetings in which further select-

ed papers are presented to specific interested delegates. One particularly enlightening session was the white matter study group which had presentations of what would be the 'ideal' group of sequences to visualise white matter disease (in other words MS for the purpose of the meeting) in under an hour. The apparent disparity between new and clever sequences and everyday clinical practice was clear, and of particular interest to me. In all the years that quantitative imaging has been with us it is disappointing how infrequently it is used in clinical neurological practice, not just in the United Kingdom. Newer and better sequences have been devised but how implementable are they or will they be in day to day practice? The appeal in the study group meeting for more involvement from clinicians was relevant. There is a danger that in amongst all the advance made in MRI technology by physicists (i.e. non-clinicians) we lose sight of what a lot of this is for (i.e. clinical benefit of patients).

Hence, it is important for clinicians, not least neurologists, to participate in the development of MR techniques so that clinically meaningful questions can be answered. This is not said to undermine the excellent research that has been and is being carried out. Using imaging models the understanding of disease pathogenesis and diagnosis and monitoring of conditions such as MS and others has undeniably improved. However, there is still, I feel, a gap that needs to be bridged in order for such techniques to be more widely used in patient management. Next year's meeting is in a less tropical but more accessible destination (Stockholm), and so long as one applies a degree of selectivity to concentrate on clinical presentations the ISMRM meeting is well worth attending. ♦

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