

# The Parkinson's Disease Non-Motor Group 3rd Annual Meeting, 2008



The Parkinson's Disease Non-Motor Group was founded to raise awareness and develop tools and protocol for the assessment of non-motor-symptoms (NMS) in Parkinson's Disease. The 3<sup>rd</sup> annual meeting of the group was held at the Royal Society of Medicine, London, on 8<sup>th</sup> March 2008. It provided delegates with numerous presentations from international experts in Parkinson's Disease. It proved to be an opportunity to review the past year's successes in the field of NMS, and another informative and invaluable day of learning.

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## **Introduction:**

The Parkinson's Disease Non-Motor Group (PDNMG) held its third annual meeting and conference at the Royal Society of Medicine, London, England, on 8<sup>th</sup> March 2008. It was attended by 150 health care professionals and offered presentations by a dazzling array of internationally renowned Parkinson's Disease specialists.

The organization was founded in 2005 by K Ray Chaudhuri, P Martinez-Martin and AHV Schapira. The mission of the PDNMG is to raise awareness and knowledge of the non-motor symptoms of Parkinson's Disease, and to develop tools for their clinical assessment.

The PDNMG focuses on a multidisciplinary approach, bringing together neurologists, geriatricians, psychologists, sleep experts, nurse specialists, cognitive experts and last but not least, patient group representatives.

## **Presentations**

PDNMG Chairman, K Ray Chaudhuri, opened the meeting and briefly discussed the prevalence of non-motor symptoms (NMS). A range of NMS including dribbling saliva, constipation, depression, sleep disorders, apathy, hallucinations and dementia complicate the lives of people with Parkinson's disease. However, even though the last 30 years have seen enormous advances in the management of the motor symptoms, the NMS complex of PD have remained relatively unexplored. Professor Chaudhuri congratulated the Parkinson's Disease community on the establishment of the Non-Motor Symptom Scale in 2007, and introduced AHV Shapira to the conference participants to chair the morning's presentations.

The first address was given by E Tolosa on the pre-clinical phase of Parkinson's Disease. He examined the correlation between Braak staging with clinical manifestation, imaging of the Substantia Nigra, and non-motor symptoms including olfactory disturbances, depression and autonomic system disorders. Professor Tolosa suggested that NMS are not prodromal but in fact part of Parkinson's Disease. He did however concede that it would be difficult to prove timing and progression in patients and called for more research in neuroprotective treatment and LRRK2-associated pathogenesis.

Professor Schapira then delivered a talk on when to start treatment of Parkinson's Disease. He discussed the 'preclinical' markers including depression and olfactory disturbances, the pathological clues, neuroimaging assessment of progression, and genetic linkages. It was highlighted that UPDRS scores decrease more slowly in patients with early diagnosis and treatment, taken from results from various studies including DATATOP, TEMPO and QE2. Professor Schapira reviewed the neuroprotective and symptom control advantages of early monotherapy and the conflicting evidence surrounding the concept. He concluded that the eventual decision must be made after a patient orientated discussion, balancing the side

effects of treatment with the reported improvements in quality of life, symptom control and disease progression.

The late morning comprised of talks by D Burn and DJ Brooks on the management of dementia in PD and the imaging of dementia and depression in PD, respectively.

D Burn was keen to examine the similarities and differences between Dementia with Lewy Bodies (DLB) with Parkinson's Disease Dementia (PDD), and discussed diagnostic criteria, management algorithms and drug treatments for PDD. He briefly reviewed Rivastigmine patches, Memantine and Anti-Cholinesterase Inhibitors as possible therapies (concluding that all were anecdotally positive albeit contentious in their effects) and then proceeded to look at drugs with multiple modes of action (Ladostigil and Adenosine receptor antagonists). Finally, D Burn addressed the various anti-amyloid strategies for PDD, such as statins (which have been shown to reduce neuronal alpha-synuclein aggregation in in-vitro models), Muscarinic-1 receptor antagonists, anti-inflammatory agents and amyloid immunization therapy.

Professor David Brooks continued on the theme of dementia, outlining the uses of FDG-PET, FP-SPECT, F-Dopa PET, Acetylcholinesterase Imaging and PET Amyloid plaque imaging in patients suffering from Parkinson's Disease, DLB and Alzheimer's Disease. PDD patients demonstrated decreased parieto-temporal metabolism levels, decreased mesocortical dopamine levels and decreased global Acetylcholinesterase levels. An interesting point was that although DLB is associated with an increase in amyloid plaque load, PDD is not – allowing clinicians to differentiate the diagnoses and therefore adapt treatment. Looking then at depression, Professor Brooks concluded that patients were more likely to demonstrate frontal lobe hypometabolism and limbic dopamine dysfunction.

The afternoon session began with a presentation by P Barone on the management of hallucinations and psychosis. After discussing the epidemiology, treatment and management, Professor Barone highlighted that: atypical anti-psychotics were recommended, long term treatment is the rule, patients with concomitant dementia with visual hallucinations should start AChE-I, and that testing cognitive function is an essential part of the clinical examination.

Following on, C Clarke offered an appraisal of drug therapy for motor and non-motor symptoms. Professor Clarke began by summarizing the shortfalls of previous trials in symptomatic early PD treatment and then introduced the ongoing PDMED trial, which looks at both the patient related quality of life and health economics. He then discussed the surgical options for PD (bilateral subthalamic stimulation) and the criteria, based on UPDRS and PDQ39 scores, by which patients are chosen. Finally, Professor Clarke looked to the future of drug therapy in PD – prolonged release Ropinirole, Safinamide, and antidyskinesia agents such as Istradefylline, an adenosine receptor antagonist. However, he was quick to temper high hopes, quoting reports of limited increases in UPDRS scores and decreases in NMS that these drugs have so far shown in patient trials.

F Stocchi continued the meeting's talks, looking at the NMS management of respiratory dysfunction and sleep problems. Because the recent trial by Pal et al,

2007, published in *Movement Disorders*, included smokers in their study, Professor Stocchi reported the early results of his own trial in 30 patients (all non-smokers) suffering from severe PD. Assessments of maximal inspiratory pressure, pulmonary function tests and dyspnoea perception in patients in 'on' and 'off' phases show interesting preliminary results. 90% of patients have difficulties when 'off' compared to 78% when 'on'. These can be explained by bradykinesia of the diaphragm and intercostal muscles, and postural problems.

Professor Stocchi then reviewed sleep problems such as akinesia, pain, vivid dreams and daytime sleepiness, all of which are highly prevalent in patients with advanced PD, and their affects on quality of life. He suggested treatments for nocturnal akinesia, rigidity and dystonia (prolonged release levodopa and COMT-I), sleep initiation problems (benzodiazepines) and sleep maintenance problems (amitriptyline, clonazepam and clozapine). Prof Stocchi ended by stressing the use of the Epworth Sleep Scale as a measure of a patient's sleep related problems, and advised the avoidance of alcohol, caffeine, amantadine, opiates and SSRIs in sufferers.

Following a short break, the afternoon continued with elegant speeches from R Brown on the management of depression and apathy in PD, and J Johnson on speech and swallowing difficulties in PD.

Professor Brown, from the Institute of Psychiatry, emphasized the importance of screening and detection of symptoms that are surrounded by stigma. He quoted NMS Scales and questionnaires, clinically rated depression scales such as the Hamilton Scale and Montgomery Scale, and self-reported depression scales. For mild depression, Professor Brown recommended anti-depressants and general measures such as anxiety management and exercise. For more severe depression, he suggested SSRIs, but called for more research into PD and Depression since there is currently no established treatment algorithm. However, ongoing randomized-controlled trials suggest the use of combined serotonin-noradrenaline therapies like venlafaxine or D2/D3 agonists such as pramipexole, for patients with treatment resistant depression with PD. However all have limited evidence of safety and tolerability, leading Professor Brown to discuss psychological means, including cognitive behavioural therapy.

In her presentation on speech difficulties, Mrs Johnson, a speech and language therapist specialising in PD, outlined the main dysarthric motor features, linking it to complications in the basal ganglia, the thalamus, and also to depression being a causative factor in emotional prosody. She reviewed the drug treatments, therapeutic devices and the management programmes (Lee Silverman Voice Treatment) available to patients. Mrs Johnson concluded by calling attention to the paucity of drug trials that use speech assessment as positive end points.

Professor P Odin then took to the stage for a topic that is the least often broached and the most forgotten symptom in the NMS spectrum. His presentation of sexual dysfunction quoted Bronner et al, 2004, who found that 68.5% of patients with PD suffered from problems, compared to 33% in a healthy group of the same mean age. While a combination of autonomic dysfunction and psychological anxiety was blamed for hyposexuality, Professor Odin recommended the involvement of gynaecological and urological teams, psychosocial counselling, anti-anxiety medication, the use of Sildenafil, and a reduction in PD medication. On the flip side, he examined the effects of long-term Levodopa and Dopamine agonist use causing hypersexuality, looking at the social and health-related quality of life issues that it raises. The ideal management in this scenario is atypical neuroleptic use, hormone therapy, and of course, a reduction in drug dose where possible.

The day came to a successful conclusion when G Macphee took to the stage to present 'Gambling, impulsive and compulsive behaviour', followed by M Visser, discussing 'Quality of life determinants in PD'. Professor Macphee outlined the progression between 'recreational', 'problem' and 'pathological' gambling (PG), drawing parallels to Obsessive Compulsive Disorder. PG is ritualistic and triggered by adverse stimulation. Whilst the source of impulsivity is dopamine activity in the Ventral Striatum, compulsivity is tracked to the Dorsal Striatum. The reward centre of the brain, the Nucleus Accumbens also shows increased dopamine release to cause increased motivation. When the entire system is abberantly fired by dopamine agonists, there is an increased motivational value of stimuli, leading to severe psychosocial and financial implications. Professor Macphee ended with a review of management. Whilst the evidence base remains poor, an individualized approach utilising neuroleptics, mood stabilizers and psychological counselling, including CBT and Gambler's Anonymous, was advised.

M Visser ended the day looking at PD from the patient's perspective. The SCOPA and ProPark scales have shown that it is incorrect to assume that curing a patient's motor problems will lead to an increase in HRQoL. Sexual, urinary, gastrointestinal and thermoregulatory problems appear to be most predictive of low HRQoL scores. Therefore, Professor Visser summarized that the treatment in the future must target the improvement of activities of daily living, psychosocial problems such as depression, and the autonomic nervous system.

### **Closing remarks**

To close the meeting, P Martin-Martinez, K Ray Chaudhuri and K Breen made a few final comments. Massive progressive has been made in the three years since a Parkinson's Disease Society survey showed insufficient perspectives in NMS. However, it appears that drug therapies being developed for release in the next five years unfortunately will not correlate to our new depths of understanding of NMS. The community has yet to find new solutions. Instead, the panel suggested that drugs will produce fewer side effects (especially with regard to hypersexuality ad compulsive behaviour) rather than an increase in efficacy. The results of a patient-reported NMSQuest study, collating over 100,000 responses, will soon be published.

The focus of the PD community will shift to improving the patient's quality of life in what Professor Martin-Martinez labelled 'the reconstruction of Parkinson's Disease'.

## **Conclusions**

In what Professor Ray Chaudhuri described as a 'unique, challenging, world-class, educational and instructive' conference, the 3<sup>rd</sup> PDNMG annual meeting was a resounding success – in part thanks to the speakers, the delegates, the assistants and the sponsors, Boehringer Ingelheim, Britannia Pharmaceuticals and Solvay Pharmaceuticals.

The valuable questions which followed many of the presentations made a significant contribution to the proceedings and ensured that lively discussion continued at the breaks between sessions. The social programme for the meeting was again a most useful feature of the meeting, with old acquaintances being renewed and new contacts nationally and internationally established. The tremendous value of this aspect of this gathering is impossible to quantify even in the present climate of assessment and documentation of achievements of such meetings.

## **References**

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