



PD MED Collaborators' Meeting Report

23rd – 24th May 2006

Jury's Inn, Tuesday 23rd May 2006

Introduction

Richard Gray welcomed delegates to this seventh meeting of the PD MED Collaborators. It was an exciting time for PD research with the establishment of the DeNDRoN Clinical Research Network. He noted how reliable quantification of the risk factors and efficacy of adjuvant treatments had led to sharp falls in cancer mortality. It was harder to measure success in neurodegenerative diseases but he believed that similar benefits could be achieved from increased research activity. To recognise the importance of non-motor symptoms, the theme of this years meeting was *Current and Future Management of Mental Health Problems in Parkinson's*.

Management of Lewy Body dementia and Parkinson's disease dementia

David Burn, Consultant Neurologist at Newcastle General Hospital gave an informative presentation on the management of Lewy Body and PD dementia. He noted the huge burden of dementia, which contributes 11.2% of years lived with disability in people over 60 years of age, more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5%) and all forms of cancer (2.4%). Dr Burn explained how PD and Lewy Body dementia form a disease spectrum and are both common and difficult to manage. Modest symptomatic benefits are possible at present but improved diagnostic criteria for PD dementia are needed – big challenges remain! Sadly for David, he had to return to Newcastle missing the drinks reception and lovely dinner.



The Birmingham Botanical Gardens

Botanical Gardens, 24th May 2006

Management of Depression in PD

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Dr Hugh Rickards opened the second day of the meeting, at the Birmingham Botanical Gardens, with a presentation entitled *Abnormal Mental States in Parkinson's disease: Recognition and Management*. Results from the EuroQol questionnaire show that up to 40% of variance in patient's overall quality of life is accounted for by depression with only 14% attributed to movement disorder. Choice of treatment was problematic and further research was needed to improve management.



Problems with dementia trial designs: experience from AD2000

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Richard Gray outlined problems in dementia trials, in particular the need to include more typical clinical populations, continue treatment for longer, to assess meaningful outcome measures and to achieve high follow-up rates. Activities of daily living, problematic behaviour, and caregiver burden were key outcomes. He also advocated wide eligibility to investigate any heterogeneity in treatment response between different diagnostic groups and disease severity. There remained many unanswered questions about drug and non-medical treatments that needed to be addressed in rigorous, independent RCTs.

Research recommendations from the NICE PD guideline

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Carl Clarke presented the seven major research recommendations to emerge from the

National Institute for Health and Clinical Excellence (NICE) guideline on the diagnosis and management of PD (www.nice.org.uk):

1. Development of neuroprotective (disease-modifying) therapies
2. Which people with PD and dementia benefit from cholinesterase inhibitors and/or memantine and is the use of these agents cost-effective?
3. Is antidepressant treatment of mild to moderate depression in PD cost effective?
4. Is occupational therapy cost effective?
5. Is physiotherapy cost effective?
6. Is NHS speech and language therapy cost effective?
7. Development of diagnostic investigations for PD and biomarkers to measure its progression.

Most attention was given to the development of neuroprotective (disease-modifying) therapies for Parkinson's disease. He outlined the problems with existing trials designs and the outcome measures that they use (see Clarke CE. *Movement Disorders* 2004;19:491-499):

- Rating scales – non-symptomatic therapy design; withdrawal studies; delayed-start design; futility studies
- Time to endpoint trials
- Imaging
- Mortality
- Quality of life.

The PD MED collaborators could successfully undertake neuroprotection, dementia and occupational therapy design trials in the future.



The Dementias and Neurodegenerative Diseases Research Network (DeNDRoN)

Professor Martin Rossor, Director of DeNDRoN gave an update on progress. DeNDRoN is one of the topic-specific networks forming part of the UK Clinical Research Network. DeNDRoN aims to facilitate the conduct of randomised prospective trials and other well-designed studies in dementia and neurodegenerative diseases, including prevention, diagnosis and treatment.

DeNDRoN would allow a sharing of resources and methodological expertise across a wide range of disabling long-term disorders, which share many common factors. It builds on the strengths already present in the UK and will increase research capacity in major neurodegenerative diseases including Parkinson's, Alzheimers, Motor Neurone and Huntington's disease.



A consortium from University College London and the University of Newcastle Upon Tyne has been appointed as the Coordinating Centre for DeNDRoN. The Director of DeNDRoN is Professor Martin Rossor, supported by Co-Director, Professor Ian McKeith and Assistant Director Piers Kotting.

Clinical studies groups are being set up in

Dementia - chair Professor Alistair Burns

Huntington's Disease - chair Professor Anne Rosser

Motor Neurone Disease - chair Professor Pam Shaw

Neuropathology and Brain Banking - chair to be appointed

Parkinson's Disease - chair Professor Andrew Lees

Primary Care - chair Dr Steve Iliffe

Development Strategy of the UK

Parkinson's Disease Society

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Steve Ford, Chief Executive of the PDS gave a very informative presentation on the PDS Research Agenda. The first question addressed was – What are people with Parkinson's looking for?

- High quality services across the country and throughout the whole pathway.
- High quality information, advice & support (helpline, websites etc.)
- Research improving quality of life for PwP and making progress towards cure.
- Sense of connection & mutual support for PwP, families and carers.

The PDS is the leading non-commercial funder of PD specific work in the U.K and has invested over £30million in research since 1969. Research priorities for the next 5 years include:

- Slowing or halting the progression of Parkinson's Disease
- Treatment of non-motor symptoms
- The establishment of an evidence-base of 'best practice' for the management of Parkinson's disease
- Implementing PD research findings into practice
- Evaluation of 'classical' (e.g. physiotherapy, speech therapy) and complementary therapies

The way forward:

- Involve both PDS members and the research community to identify key areas of research
- Facilitate new researchers
- Be more proactive
- Be more outcome orientated
- Improved communication and making better use of the outcomes

The ultimate aim is to ensure that people with Parkinson's live a life that is free of the symptoms of the condition, however that may be achieved for the individual.



Lunch

PD MED Update

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Tom Boodell, PD MED Trial Coordinator, update participants on PD MED progress and other trial issues. Recruitment stood at 1157, 887 early disease and 270 later disease patients. 6-monthly recruitment to the trial has increased steadily but there was still a need to increase recruitment to reach the target of 30 patients monthly. PD MED is the largest ever trial in PD medication and now has nearly 400 more patients than the previous largest (Datatop study – 800 patients). The top 3

recruiting regions were West Midlands (255 patients), South West (210) and North West (117).



The top individual recruiting centres are:

1. Royal Devon & Exeter – 134 patients
2. Fairfield General , Bury – 110 patients
3. City Hospital, Birmingham – 79 patients
4. Leicester General – 60 patients
5. Aberdeen Royal – 46 patients

Form completion rates remained high, for both patients and clinicians, and this too needed to be maintained to allow reliable assessment of long-term clinical and cost-effectiveness.

Table 1: PD MED form completion rate

Form	Patient PDQ39	Clinician Annual Review
Baseline	99%	-
6 month	93%	-
1 year	93%	90%
2 year	90%	89%
3 year	88%	87%
4 year	82%	87%

Collaborators were informed that an extension application had been submitted to HTA which, if successful, would allow PD MED recruitment to be extended until December 2007 and follow-up to 2011. But, good monthly recruitment figures over the next few months are vital if the extension is to be granted.

PD MED Preliminary analyses and discussion – Natalie Ives

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Natalie Ives, Principal Statistician for the PD MED trial, then presented some preliminary findings from the PD MED data analyses. The talk began with a look at the PD MED patient demographics:

Table 2: PD MED Patient Demographics

	Early (N=875)	Later (N=267)
Mean age	70	73
% male	64%	63%
Duration of PD (yrs)	0.7	6.2
Hoehn & Yahr 1-1.5	(46%)	(9%)
2	(31%)	(28%)
≥ 2.5	(23%)	(63%)

In early disease 78% of clinicians were willing to randomise to MAOBI with the breakdown of MAOBIs prescribed as follows:

- Oral Selegiline – 74%
- Sub-lingual Selegiline – 19%
- Rasagiline – 5%
- Other/Unknown – 2%

The breakdown of planned Dopamine Agonist treatment was as follows:

- Ropinirole – 54%
- Pramipexole – 20%
- Bromocriptine – 8%
- Cabergoline – 7%
- Pergolide – 6%
- Piribedil – 3%
- Other/Unknown – 2%

Similar patterns of DA and MAOBI use were seen in later disease with the breakdown of planned COMTI being:

- Entacapone – 93%
- Stalevo – 1.5%
- Tolcapone – 0.5%
- Other/Unknown – 5%

Outcome measures were performing well with PDQ-39 and EuroQol EQ-5D showing sensitivity to change. (see [presentation slides](#)). Numbers of follow-up events were increasing: of the 603 early disease patients who have completed at least one follow up assessment, 102 had developed motor complications, 20 developed dementia, 14 are in institutional care and 57 have died.

Of 185 patients in the later disease arm, 23 have developed dementia, 17 are in institutional care, 2 are being considered for surgery and 34 have died

In summary, PD MED is accruing a lot of interesting data and will provide a unique opportunity to investigate which class of drug provides the most benefits with the least side effects for people with Parkinson's disease

PD GEN Update

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Dr Carl Clarke updated the collaborators on progress in the PD GEN study. At the time of the meeting, 488 samples had been obtained from 297 patients and 191 carers. Dr Clarke emphasised the importance of continuing to enter patients and carers into the PD GEN study to increase the sample size.

PD GEN Preliminary analyses and discussion – Prof Karen Morrison

[Click here for presentation slides](#)

In addressing the key question of causation of PD it is likely that both genetic and environmental factors are important. In this talk Professor Morrison reviewed some of the data on the 6 genes in which mutations have been identified in mendelian forms of PD: α -synuclein and LRRK2 to cause dominant disease; parkin, UCHL1, DJ-1 and PINK1 in causing recessive disease. Key features reported in the last few years were highlighted e.g. reports that abnormalities of α -synuclein copy number seem to give disease with a rapid disease progression; an update of data on the normal cellular function of α -synuclein and how this may be altered by mutation; the recent work that LRRK2 mutations, particularly the Gly2019Ser mutation, are relatively common in typical late onset PD and that LRRK2 mutation carriers have varying neuropathology; the fact that autosomal recessive parkin mutations are relatively frequent in early onset PD.

In discussing genetics and PD Professor Morrison also emphasised the importance of genetic susceptibility factors acting along with environmental agents to cause disease. In deciding which genes to study for susceptibility, genes can be targeted based on their known role in mendelian forms and also on plausible functional hypotheses. The era of whole genome scanning to find susceptibility loci, in which no prior knowledge of putative function is assumed, has also now arrived. Having large numbers of DNA samples from clinically well-characterised patients and controls is key to the success of susceptibility scans. It is here that the great strength of PD GEN lies. We have all the clinical information available from PD MED and PD SURG linked to the PD GEN samples. PD GEN has the potential to be a very valuable resource for

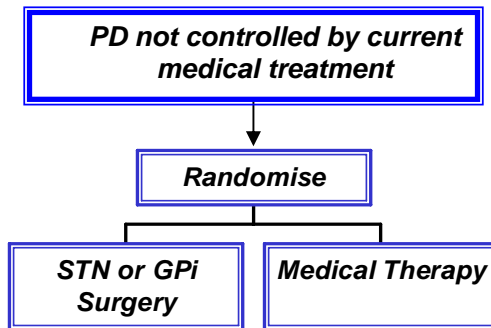
such susceptibility studies – but we need large numbers of samples (probably around 1000 cases and suitably matched controls). Once collected, PD GEN samples will be made available through the MRC for use by the whole research community. Collaborators in PD MED and PD SURG are strongly encouraged to enrol their patients in PD GEN.

PD SURG Update

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Caroline Rick, PD SURG Trial Coordinator, then gave an update on the progress of the PD SURG trial, which aims to determine whether or not early surgery provides more or less effective long-term control than medical therapy (with surgery deferred for as long as possible).



At present there are 299 participants randomised into PD SURG study from 12 centres around the country. This makes it by far the biggest ever RCT in surgery for Parkinson’s disease. The top recruiting centres are:

- Queen Elizabeth Birmingham – 62 patients
- Frenchay Hospital, Bristol - 46 patients
- Walton Centre, Liverpool - 40 patients

The results of PD SURG will determine whether surgery is a beneficial and cost-effective intervention and, if so, the optimal timing.

PD Occupational Therapy Pilot Update

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Alex Furnmston, Trial Coordinator, then gave an update on the progress of PD OT, a randomised controlled trial of occupational therapy in people with PD. The aim of the PD OT Pilot Study is to obtain data to allow accurate sample size estimation and identify suitable outcome measures for a high quality trial of community

occupational therapy for PD. In particular, the effects of OT on functional independence, mobility, carer strain, quality of life and costs will be assessed.

The PD OT Pilot aims to recruit 50 patients with PD who may benefit from occupational therapy. Half the patients will be randomized to receive OT (6 x 45 minute sessions over 2 months), with the other half receiving standard PD treatment (occupational therapy deferred). Seven hospitals from the West Midlands region are taking part and recruitment currently stands at 27 patients.

Closing Remarks

Dr Clarke closed the meeting by thanking everyone for their attendance and reiterating the importance of keeping the recruitment rate for PD MED & PD GEN as high as possible.