Institution: King's College London

Unit of Assessment: UoA4 – Psychology, Psychiatry & Neuroscience

Title of case study: 18: Enhancing clinical management of non-motor symptom burden in Parkinson's Disease

1. Summary of the impact

Parkinson's Disease is a disabling disorder affecting 1 in 500 people in the UK. King's College London (KCL) researchers discovered that non-motor symptoms are a key determinant of quality of life for patients with Parkinson's Disease but found these were rarely assessed or treated. KCL researchers developed the first patient-reported questionnaires allowing clear documentation of different non-motor symptoms. These KCL-designed scales empowered patients to report these symptoms and receive appropriate treatments and led to the implementation of patient outcome-based policy-making in England and internationally. They also placed important symptoms for a patient's quality of life as a key outcome in large-scale clinical trials for Parkinson's Disease.

2. Underpinning research

Affecting 1 in 500 people in the UK, Parkinson's Disease is the second commonest chronic neurodegenerative condition with around 127,000 people living with the condition, one in 20 of whom is under 40. While historically defined by motor symptoms, research at Institute of Psychiatry, King's College London (KCL) highlighted the clinical importance of non-motor symptoms including dizziness, sleep problems and pain. KCL researchers, led by K Ray Chaudhuri (2006-present, Professor of Neurology and Movement Disorders) and Richard Brown (1998-present, Professor of Psychology), along with colleagues from the multidisciplinary international Parkinson's Disease Non-Motor Group (PDMNG), established by Prof Chaudhuri, were the first to develop and validate non-motor symptoms tools to allow declaration and quantitation of this complex range of symptoms.

KCL studies in the UK and Europe, in conjunction with Parkinson's UK, showed that in day to day life patients rated non-motor symptoms as more troublesome than motor problems. However, they also said that as their non-motor symptoms were never assessed and so remained untreated despite affecting their quality of life (1). KCL researchers led an international project that developed, tested and validated the NMS Questionnaire (NMSQuest), the first ever patient screening tool to assess common Parkinson's Disease non-motor symptoms. This simple, brief, 30 question tool allows patients to self-report the presence/absence of symptoms such as dribbling, incontinence, mood changes, sexual difficulties and vision or hearing changes. The initial 2006 study, involving 123 patients and 96 controls across Europe, USA and Japan and provided evidence of its validity and utility as well as endorsement by patients and family members (2). The next year a KCL-led international study of 545 patients provided cross-cultural validation of NMSQuest and indicated an average 9 to 12 different non-motor symptoms for each patient even in early Parkinson's Disease (3). This was the first time the extent of non-motor symptoms in Parkinson's Disease patients, regardless of disease duration, had been quantified and it highlighted the scale and significance of the problem. KCL then led a European multicentre study of NMSQuest use in routine clinical practice, providing the first opportunity for patients to discuss previously undeclared symptoms to health care professionals (1).

Whilst NMSQuest provides a screening tool for non-motor symptoms, it does not provide a measure of non-motor symptom severity. KCL led an international Parkinson's Disease Non-Motor Group study to develop and validate the Non-Motor Symptoms Scale (NMSS), a 30-item scale containing nine dimensions including cardiovascular symptoms, sleep, cognition, attention and gastrointestinal problems. This holistic, grade-rating tool for Parkinson's Disease was extensively validated with robust clinimetrics in Europe, Asia, South America, Israel and the USA in a total of 950 cases (4,5). It provides a key predictor of health-related quality of life (6). Importantly, these studies showed that NMS severity and burden was only modestly associated with motor symptoms severity and disease progression, suggesting the importance of non-motor symptoms as an independent disease dimension.

As many Parkinson's Disease patients have mild-moderate sleep disturbances, in 2002 KCL researchers and collaborators also developed and refined the Parkinson's disease sleep scale (PDSS). This scale, whose development involved143 patients and 137 controls, addresses 15

commonly reported symptoms associated with sleep disturbance in Parkinson's Disease (7). In 2011, the PDSS-2 extended the PDSS to become a frequency measure scale with five categories and to encompass unmet needs such as restless legs syndrome, akinesia, pain and sleep apnea. This was validated by 113 patients in London, Austria and Germany (7, 8).

3. References to the research

1. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The non declaration of non motor symptoms of Parkinson's disease to health care professionals: an international study using the non motor symptoms questionnaire. Mov Disord 2010;25(6):704-9. Doi: 10.1002/mds.22868 (45 Scopus citations)
2. Chaudhuri KR, Martinez-Martin P, Schapira AHV, et al. International multicentre pilot study of the first comprehensive self-completed non motor symptoms questionnaire for Parkinson's disease: The NMSQuest study. Mov Disord 2006;21(7):916-23. Doi: 10.1002/mds.20844 (196 Scopus citations)
3. Martinez-Martin P, AHV Schapira, Chaudhuri KR, et al. Prevalence of non motor symptoms in Parkinson's disease in an international setting; study using non-motor symptoms questionnaire in 545 patients. Mov Disord 2007;22(11):1623-29. Doi: 10.1002/mds.21586 (130 Scopus citations)
4. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: Results from an international pilot study. Mov Disord 2007;22(13):1901-11. Doi: 10.1002/mds.21596 (128 Scopus citations)
5. Martinez-Martin P, Rodriguez-Blazquez C, Chaudhuri KR, et al. International study on the psychometric attributes of the non-motor symptoms scale in Parkinson disease. Neurology 2009;73(19):1584-91. Doi: 10.1212/WNL.0b013e3181c0d416 (47 Scopus citations)
6. Martinez-Martin P, Rodriguez-Blazquez C, Chaudhuri KR, et al. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. Mov Disord 2011;26(3):399-406. Doi: 10.1002/mds.23462 (65 Scopus citations)
7. Chaudhuri RK, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:629-35. Doi: 10.1136/jnnp.73.6.629 (195 Scopus citations)
8. Trenkwalder C, Kohnen R, Chaudhuri KR, et al. Parkinson's disease sleep scale--validation of the revised version PDSS-2. Mov Disord 2011;26(4):644-52. Doi: 10.1002/mds.23476 (26 Scopus citations)

Grants

- 2002-2007 PDLIFE, a multicentre UK wide prospective audit of changes in quality of life in people with Parkinson's in response to treatment over 5 years PI: K R Chaudhuri and members of the UK PDLIFE committee. Parkinson's Disease Society £ 114,000
- 2006-2008. Parkinson's Disease Non Motor Questionnaire/Scale Validation International Pilot Coordinator Posts. PIs: K Ray Chaudhuri and the PDNMG. Pfizer and Boehringer Ingelheim Educational Grant and Glaxo Smith Kline Medical Fellowship. £139,000
- 2007-2010. Defining the palliative care needs of people with late stage Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. PIs: PN Leigh, L Turner-Stokes, I Higginson, K Ray Chaudhuri, C Clough. Department of Health, UK. £228 676
- 2006-2011. Development a nurse-led intervention for carers of Parkinson's disease patients PIs: RG Brown, I Higginson, PN Leigh, KR Chaudhuri. Edmond J Safra Foundation. £180,000

4. Details of the impact

Researchers at KCL developed the non-motor symptoms questionnaire (NMSQuest), the Non-Motor Symptoms Scale (NMSS) and the Parkinson's Disease Sleep Scale (PDSS). Non-motor symptoms are key determinants of quality of life in Parkinson's Disease, yet prior to KCL work, there were no bedside tools to address the impact of these symptoms, no tools to allow self-declaration of symptoms or any grade-rating tools for overall non-motor symptom scoring.

Parkinson's disease associations recommend the use of NMSQuest and NMSS: Parkinson's UK, the country's foremost Parkinson's Disease support and research charity, recently commissioned a survey of 10,101 Parkinson's Disease patients using NMSQuest. They confirmed that non-motor symptoms increase with disease duration; that younger people are more greatly impacted by them and that high NMSQuest scores are correlated with worsening quality of life scores (1a). Parkinson's UK found the NMSQuest so useful that it champions the scale on their

website with recommendations that patients complete it ahead of visiting a health care professional (1b). Also their 'Professional's Guide to Parkinson's Disease' recommends use of NMSQuest to health care professionals including GPs, nurses, physiotherapists and social workers (1c).

Both NMSQuest and NMSS are highlighted in an article on 'Life With Parkinson's' aimed at healthcare professionals, patients, carers and the media, written by KCL researchers for the European Parkinson's Disease Association, an organisation which "advocate for the rights and needs of people with Parkinson's Disease and their families." An accompanying article discusses how non-motor symptoms lead to disability and an overall increase in the cost of Parkinson's care (1d). Following a systematic assessment by a professional review panel, all 3 scales are recommended to clinicians, scientists and health care professional by the Movement Disorders Society, an international professional society with over 4,100 members from over 90 countries (1e).

Use of NMSQuest in practice: The Scottish Intercollegiate Guidelines Network (SIGN) 2010 guidance regarding 'Diagnosis and pharmacological management of Parkinson's Disease' discusses how non-motor symptoms contribute "to a very significant curtailment of social activity." The NMSQuest is included as an appendix and they recommend that healthcare professionals should highlight its availability to patients (2a). These SIGN guidelines provide reference points for clinical practice in England and Wales. For instance, the Parkinson's Disease Map of Medicine cites them when listing identifying non-motor symptoms (2b). While Commissioning Pathways were in effect in England and Wales (up until Spring 2013), the Department of Health (DH) included NMSQuest to assess quality of life in its 'Elective Care Commissioning Pathway for Parkinson's Disease' and the '18-week Commissioning Pathway for Tremor in Parkinson's Disease' (2c). The NMSQuest is more recently included in the DH's Payments by Results Guidance to all Trusts in the UK for 2013-2014 (2d).

Worldwide use of NMSQuest: In 2010, the American Academy of Neurology, an international professional association of more than 26,000 members, produced Practice Guidelines that recommended the NMSQuest be used to "assist in screening and early identification of non-motor symptoms" (3a). NMSQuest and NMSS are also recommended in an e-textbook on Parkinson's Disease aimed at US healthcare professionals produced by Projects in Knowledge, a certified Continuing Medical Education company who provide approved professional development tools (3b). The Parkinson Society Canada also produces English and French versions of a non-motor symptoms guide, aimed at family physicians, which highlights the use of NMSQuest. Physicians are "encouraged to copy the questionnaire and use it for patient care" as it can help "pick up important treatable manifestations of the disease" (3c). Reflecting international demands for the scales, the MAPI Institute, an international company that advances the worldwide use of patient-reported and clinical assessments, has translated and linguistically validated PDSS (14 European, 2 Asian languages and Afrikaans) and PDSS-2 (4 languages). These are available free for non-profit researchers and healthcare professionals and for a fee for use in for-profit trials (3d).

KCL scales improve the chances of new treatment - use of NMSS in clinical trials: Before the development of the scales the importance of non-motor symptoms was unknown and therefore not a treatment target. Following the rigorous development of the scales, the efficacy of a patient valued target could be measured and non-motor endpoints are now incorporated into international clinical trials for Parkinson's Disease medications. The leading US funder of neurological clinical studies, the National Institute of Neurological Disorders and Stroke, recommends all 3 scales for Parkinson's Disease research (4a). In the recent RECOVER study, sleep and nocturnal disability measured by PDSS-2 became the target for a new skin patch version of the dopamine agonist rotigotine. In the same study fatigue and apathy were measured using NMSS. The skin patch for nighttime problems is now recommended for this previously identified but unmet problem (4b,c).

Wide reaching international dissemination: Dissemination of information about the non-motor symptom tools has occurred in the UK and abroad, to patients, carers and the wider public. For instance, the Parkinson's Disease Foundation, a leading US charity funding research and providing information for patient's and carers, broadcast a seminar by Prof Chaudhuri to 16 countries on the recognition, assessment and treatment of under-recognised non-motor symptoms. As of June

2013 it had received 885 listeners (5a). Additionally, Prof Chaudhuri is featured on the Parkinson's UK website as an expert in non-motor symptoms and he participated in an online Q&A where NMSQuest and PDSS are recommended (5b). KCL research on non-motor symptoms of Parkinson's Disease was also discussed by Prof Chauduri on BBC Radio 4's 'Inside Health' programme on Feb 12th 2012. This nationwide broadcast is available online as a podcast (5c).

5. Sources to corroborate the impact

1. Parkinson's disease associations recommend the use of NMSQuest and NMSS

a. Breen KC, et al. J Neural Transm. 2013;120(4):531-5. Doi: 10.1007/s00702-012-0928-2
b. Parkinson's UK: NMSQuest for patients: http://www.parkinsons.org.uk/content/non-motor-symptoms-questionnaire
c. Parkinson's UK: Professional's Guide to Parkinson's Disease (pp 3,22,26,60): http://www.parkinsons.org.uk/sites/default/files/publications/download/english/b126_professionalsguide.pdf
d. European Parkinson's Disease Association
   - Life With Parkinson's: http://www.epda.eu.com/en/parkinsons/life-with-parkinsons/part-2/introduction/
   - Economic Consequences of Parkinson's Disease: http://www.epda.eu.com/en/parkinsons/life-with-parkinsons/part-2/economic-consequences-of-parkinsons-disease/
e. Movement Disorders Society Website: www.movementdisorders.org/publications/rating_scales/

2. Use of NMSQuest in practice

a. SIGN Guidelines on Diagnosis and Pharmacological Management of Parkinson's Disease (pp 8, 38, 53): http://www.sign.ac.uk/pdf/sign113.pdf
b. Map of Medicine for PD: http://healthguides.mapofmedicine.com/choices/pdf/parkinson_s_disease1.pdf
c. Elective Care Commissioning Pathway - Parkinson's Disease 2008: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_122474.pdf
d. DoH's Payment by Results Guidance for 2013-2014 (p.103) https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf

3. Worldwide Use of NMSQuest

a. Zesiewicz TA, et al. Neurology 2010;74(11):924-31. Doi: 1212/WNL.0b013e3181d55f24
b. Projects in Knowledge e-textbook: Early Diagnosis and Comprehensive Management: http://lmt.projectsinknowledge.com/Activity/index.cfm?showfile=b&jn=2094&sj=2094.06&i=8&sc=2094.06.2
c. Parkinson Society Canada. Non-motor symptoms of Parkinson's Disease (pp 3,41,42): http://www.parkinsonclinicalguidelines.ca/sites/default/files/PhysicianGuide_Non-motor_EN.pdf
d. MAPI Institute PDSS and PDSS-2 translations
   - http://www.proqolid.org/instruments/parkinson_s_disease_sleep_scale_pdss?fromSearch=yes&text=yes
   - http://www.proqolid.org/instruments/parkinson_s_disease_sleep_scale_2_pdss_2?fromSearch=yes&text=yes

4. Use of NMSS in Clinical Trials

a. National Institute of Neurological Disorders and Stroke Parkinson's Disease CDE Working Group: http://www.commondataelements.ninds.nih.gov/PD.aspx#tab=Data_Standards
b. Chaudhuri KR, et al. Parkinsonism Rel Disord 2013;19:660-5. Doi: http://dx.doi.org/10.1016/j.parkreldis.2013.02.018
c. Trenkwalder C, et al. Mov Disord 2011;26(1):90-9. DOI: 10.1002/mds.23441

5. Wide reaching international dissemination

a. Parkinson's Disease Foundation, USA. PD Expert Briefing: Under-recognized Nonmotor Symptoms of Parkinson's Disease. Broadcast 12.3.2013: http://www.pdf.org/parkinson_briefing_nonmotor
b. Parkinson's UK, online Q&A: Non-motor symptoms in Parkinson's (May 2012): http://www.parkinsons.org.uk/content/qa-non-motor-symptoms-parkinsons
c. BBC Radio 4. Inside Health with Mark Porter. Broadcast 12.2.2013. From 21:20: http://www.bbc.co.uk/programmes/b01qjb1t