OUR EXPERTS HIGHLIGHT THE MOST IMPORTANT RESEARCH ARTICLES ACROSS THE SPECTRUM OF TOPICS RELEVANT TO THE FIELD OF NEURODEGENERATIVE DISEASE MANAGEMENT

Expert panel: Susan H Fox, Movement Disorder Clinic, Toronto Western Hospital, and Division of Neurology, University of Toronto, ON, Canada; Philippe Huot, Movement Disorder Clinic, Toronto Western Hospital, and Division of Neurology, University of Toronto, ON, Canada; Brad Dickerson, Massachusetts General Hospital and Harvard Medical School, MA, USA; Dag Aarsland, Alzheimer's Disease Research Center, Karolinska Institutet, Stockholm, Sweden; Niklas Mattsson, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Sweden; Theresa A Zesiewicz, University of South Florida, Tampa, FL, USA

Richard IH, McDermott MP, Kurlan R et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 78(16), 1229–1236 (2012).

Non-motor symptoms, such as depression, are being increasingly recognized as important manifestations of Parkinson's disease (PD). Depression, for instance, may affect over 50% of PD patients with long-standing disease [1]. While there are several agents used to treat depression in the non-PD population, surprisingly few trials with antidepressants have been performed in the PD population. Those that have been performed have used small numbers of subjects, often with equivocal results. In particular, the comparative benefits of different types of antidepressants in PD are unknown. The Study of Antidepressants in PD (SAD-PD) is the first large randomized controlled trial to investigate the comparative effects of a selective serotonin reuptake inhibitor (SSRI) versus a mixed serotonin and nor-adrenaline reuptake inhibitor (SNRI) on PD depression. The study was a 12-week, randomized, placebo-controlled, double-blind, 'double-dummy' Phase III study, which enrolled 115 PD patients with depression. Participants received either

the SSRI, paroxetine (maximum of 40 mg daily, mean dosage 24 ± 11 mg at the end of the study), the SNRI, venlafaxine extended release (XR; maximum of 225 mg daily, mean dosage 121 ± 75 mg at the end of the study) or placebo. In comparison with placebo, both paroxetine and venlafaxine XR reduced depression severity, as assessed with the Hamilton Rating Scale for Depression (decrease of 6.2 points with paroxetine and 4.2 points with venlafaxine XR). Both paroxetine and venlafaxine XR had beneficial effects on secondary depression outcome variables (Montgomery–Åsberg Depression Rating Scale, Beck Depression Inventory II and Geriatric Depression Scale) relative to placebo. Perhaps surprisingly, neither paroxetine nor venlafaxine XR had any effect on quality of life (Parkinson's Disease Questionnaire-39). Neither paroxetine nor venlafaxine XR had a detrimental effect on motor function (Unified Parkinson's Disease Rating Scale part III), and both treatments improved bulbar function relative to placebo. Paroxetine, but not venlafaxine XR, had a favorable effect on insomnia, when compared with placebo. Sitting blood pressure was significantly higher in the venlafaxine XR group at the end of the study when compared with the initial visit.

The SAD-PD study aimed to recruit 228 patients, but stopped after 115 subjects

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were enrolled, due to difficulty in recruitment. Nevertheless, this study is the largest randomized, placebo-controlled trial to date in PD patients with depression and provides Class I evidence that both paroxetine and venlafaxine XR are effective in treating depression in PD. The study was also insightful in suggesting that improving depression may not necessarily be associated with an improvement in overall quality of life, as several factors, such as motor symptoms, are also likely to impair quality of life. Although there was no apparent superiority between the drugs, the results suggest that paroxetine may be more suited for depressed PD patients experiencing insomnia, whereas venlafaxine XR may be of additional value in the treatment of depressed PD patients with hypotension, although further studies are needed to validate these hypotheses. Lastly and importantly, none of the two active treatments had a deleterious effect on motor function. Further studies are still needed to compare other antidepressant classes such as tricyclic antidepressants with SNRIs and SSRIs to determine comparative benefit versus side-effect profiles in PD subjects with depression.

– Written by Philippe Huot
& Susan H Fox

Reference

- 1 Hely MA, Morris JG, Reid WG, Trafficante R. Sydney multicenter study of Parkinson's disease: non-L-DOPA-responsive problems dominate at 15 years. *Mov. Disord.* 20(2), 190–199 (2005).

Boeve BF, Boylan KB, Graff-Radford NR et al. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain* 135(Pt 3), 765–783 (2012).

In late 2011, two collaborative groups reported the identification of a novel genetic mutation in families, known as the *C9ORF72* expansion, in which individuals developed frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS) or, in some cases, both clinical syndromes.

This paper reports details of the demographic, clinical, neuropsychological and imaging characteristics of patients with this mutation; some cases with neuropathology were also described. The authors refer to these patients as having c9FTD/ALS. Most cases had at least one relative with ALS or dementia, although a small number of apparently sporadic onset cases were reported.

Of the 63 symptomatic individuals with the mutation, age of symptom onset was quite variable, ranging from 33 to 72 years (median 52 years); survival was also notably variable, ranging from 1 to 17 years (most died within 7 years of symptom onset). Behavioral variant FTD was the most common clinical phenotype (nearly 50%), followed by ALS (~30%), and finally FTD/ALS (~20%). Notably, no individual exhibited a primary progressive aphasia syndrome. Parkinsonism was common, with an akinetic-rigid phenotype (without tremor) in 35% of examined subjects. Neuropsychological testing showed a profile of slowed processing speed, complex attention/executive dysfunction and impairment in rapid word retrieval. Approximately a third of subjects did not exhibit impairment on initial neuropsychological testing. Half of the patients had prominent psychosis (delusions or hallucinations), and all exhibited appetite or eating behavioral abnormalities.

Neuroimaging studies showed bilateral frontal abnormalities, with more variable degrees of parietal with or without temporal changes; in contrast to cases with genetic mutations in progranulin, no case of c9FTD/ALS had strikingly focal or asymmetric findings. In the 14 patients with autopsy material available, TDP43 pathology was present. Motor neuron degeneration was detected in nine patients, including five without signs of motor neuron disease during life. In summary, while this genetic form of FTD/ALS exhibits variability, most cases with this mutation have a characteristic spectrum of demographic, clinical, neuropsychological, neuroimaging and especially neuropathological findings. This set of findings represents a major step forward in the fields of FTD and ALS, and underscores the value

of the establishment of an infrastructure for the systematic collection of clinical and pathological data in patients with these disorders so that when new genetic mutations are identified, the clinical and pathological phenotypes of patients with the genotype can be rapidly reported.

– Written by Brad Dickerson

Schrijvers EM, Verhaaren BF, Koudstaal PJ, Hofman A, Ikram MA, Breteler MM. Is dementia incidence declining? *Neurology* 78(19), 1456–1463 (2012).

The prevalence of dementia has been estimated to double every 20 years due to demographic changes. However, this prediction assumes no change in incidence. With changing lifestyles and preventive measures, dementia incidence may, however, change. For example, stroke incidence has been shown to decrease [1]. In the Rotterdam Study, one of the world's most important epidemiological dementia studies, the 10-year incidence of dementia was compared in two dementia-free cohorts aged 60–90 years from 1990 (n = 5277) and from 2000 (n = 1769). Patients were prospectively examined according to a standardized protocol every 3–4 years.

Screen-positive cases (i.e., those with an Mini Mental State Examination score <26 or Geriatric Mental State organic level score >0 at follow-up) underwent cognitive examination or, if needed, neuropsychological examination. Although not all comparisons were statistically significant, the findings consistently suggested a reduction in age-adjusted dementia incidence of 25% across age-groups in the 2000 cohort compared with the 1990 cohort. This finding was paralleled by larger brain volumes and smaller white-matter lesion volumes and lower frequencies of cortical or lacunar infarcts on MRI. Similarly, the 2000 cohort was better educated, and the use of preventive treatments such as lipid-lowering and anti-thrombotic agents was higher. Whereas mortality was lower, the frequency of diabetes and hypertension was higher in the 2000 cohort compared with the 1990 cohort.

These findings, consistent with some previous reports, support the hypothesis that dementia incidence is declining, possibly due to lifestyle changes and drug strategies to reduce vascular and other risk factors for dementia.

– Written by Dag Aarsland

Reference

- 1 Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol.* 8(4), 355–369 (2009).

Favilla CG, Ullman D, Shukla AW, Foote KD, Jacobson CE, Okun MS. Worsening essential tremor following deep brain stimulation: disease progression versus tolerance. *Brain* 135, 1455–1462 (2012).

Essential tremor (ET) is one of the most common movement disorders in the world, but treatment of the disorder can be challenging. It is estimated that 30–50% of ET patients do not respond to medical management. Deep-brain stimulation (DBS) of the ventral intermedialis nucleus (VIM) of the thalamus is a therapeutic modality that has become increasingly utilized to treat ET patients with severe tremor. One concern about VIM–DBS treatment is the apparent loss of surgical efficacy in a minority of patients over time. It is unclear whether this phenomenon can be attributed to tolerance to the procedure, disease progression or suboptimal lead placement.

Favilla *et al.* sought to determine whether tolerance or disease progression was responsible for the apparent loss of surgical efficacy in 28 patients who received VIM–DBS and 21 control subjects in this retrospective study. In both groups, the rate of tremor progression was found to be consistent with natural disease progression. Seven of the 28 patients in the VIM–DBS group were isolated from the treatment cohort due to evidence of secondary progression of tremor, defined as an increase in the ‘off’ tremor rating scale

motor score between 6 and 36 months following surgery. Six of the seven subjects continued to experience a sustained benefit of stimulation at the study end point, suggesting potential disease progression rather than tolerance; one patient was found to have slightly suboptimal lead placement. The authors conclude that DBS tolerance may be over-reported in the literature, and that tolerance attributed to VIM–DBS must be separated from disease progression by more careful focus on lead location, trends in off-stimulation scores, clinical benefits and side effects that occur during programming.

– Written by Theresa A Zesiewicz

Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson’s disease occurring with Type 2 diabetes in a Taiwanese population cohort. *Parkinsonism Relat. Disord.* 18(6), 753–758 (2012).

Parkinson’s disease (PD) is a common neurodegenerative disease with a complex pathogenesis. The role of diabetes as an antecedent cause of PD has been controversial, with both positive and negative studies appearing in scientific literature. Wahlqvist and his colleagues sought to evaluate whether Type 2 diabetes mellitus (T2DM) and commonly used oral anti-hyperglycemic agents (OAAs) were associated with the development of PD in the Taiwanese population. Using data from a representative cohort of 800,000 people that was obtained between 1 January 1996 and 31 December 2007 from the Taiwan National Health Insurance database, the authors identified the presence or absence of T2DM and the use of OAAs. Patients with T2DM were matched with diabetes mellitus-free patients to determine PD incidence. Information about the presence or absence of OAAs in T2DM patients who did not have PD was also obtained.

The study found that incident PD increased 2.2-fold in T2DM patients in the Taiwanese population. Sulfonylureas

further increased the risk by 57%, which was avoided by combination use with metformin. Metformin (Glucophage® [Bristol-Myers Squibb], a member of the biguanides) appeared to provide protection against PD when sulfonylureas were used in both genders. Study limitations include the use of diagnostic codes for disease identification, the absence of information concerning T2DM severity, and whether OAA use could have been a surrogate for other risk factors. Nonetheless, the study provides important information about a possible risk factor for PD.

– Written by Theresa A Zesiewicz

Toledo JB, Brettschneider J, Grossman M *et al.* CSF biomarkers cutoffs: the importance of coincident neuropathological diseases. *Acta Neuropathol.* 124(1), 23–35 (2012).

With the development of potentially disease-modifying drugs for Alzheimer’s disease (AD), there is a boom in the interest of methods for early and accurate AD diagnosis, in order to optimize clinical patient management and facilitate selection or stratification of study participants in trials. The cerebrospinal fluid (CSF) biomarkers β -amyloid₄₂, total-tau and phosphorylated tau reflect pathological processes in the CNS and are strong candidates for AD diagnostic methods. However, the use of these measurements is complicated by the fact that a large proportion of patients with neurodegenerative diseases show signs of combined pathologies with, for example, AD and coincident frontotemporal lobar degeneration, which may contribute to heterogeneity both in clinical presentation and in responsiveness to therapy. Since the clinical diagnosis of mixed pathologies is prone to error, neuropathological studies are needed to validate the performance of diagnostic biomarkers in these patients. Doing precisely this, the study by Toledo *et al.* is a valuable contribution to the literature. In 142 neuropathologically diagnosed patients (81% overall agreement with clinical diagnosis), CSF β -amyloid₄₂,

total-tau and phosphorylated tau had high diagnostic accuracy for AD, but lower diagnostic accuracy for frontotemporal lobar degeneration. Most patients with AD and a coincident other pathology (27% of the subjects) were classified as having AD by biomarker tests, which underscores the need for novel biomarkers to pin-point non-AD pathology in dementia patients. Finally, the use of clinical instead of neuropathological diagnosis underestimated the performance of CSF biomarkers, reminding us of the importance to use neuropathological confirmation in studies whenever possible.

– Written by Niklas Mattsson

Pottier C, Hannequin D, Coutant S et al. High frequency of potentially pathogenic *SORL1* mutations in autosomal dominant early-onset

alzheimer disease. *Mol. Psychiatry* doi:10.1038/mp.2012.15 (2012) (Epub ahead of print).

Although analysis of the genes *PSEN1*, *PSEN2* and *APP* identifies a disease-causing mutation or duplication in most patients with early onset Alzheimer's disease (AD), some patients with autosomal dominant forms of AD have no changes in these genes, indicating that additional AD-causing genes remain to be discovered. The development of novel genetic technology is now advancing this field forward. Using exome sequencing in 29 unrelated patients with a history of autosomal dominant early onset AD without mutations in *PSEN1*, *PSEN2* or *APP*, Pottier *et al.* identified (different) mutations in the *SORL1* gene in seven patients. This provides a strong case for *SORL1* mutations as a direct cause of rare cases of AD. The finding is

particularly interesting since *SORL1* has previously been linked to β -amyloid trafficking and cholesterol metabolism, which are biological pathways important for AD. The importance of *SORL1* for the large majority of AD patients having sporadic AD may be interesting to explore further.

– Written by Niklas Mattsson

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