JOURNAL WATCH

For reprint orders, please contact: reprints@futuremedicine.com

Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of neurodegenerative disease management

Expert panel: Dag Aarsland, Karolinska Institutet, Alzheimer's Disease Research Centre, Stockholm, Sweden; Henrik Zetterberg, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Sweden; Anthony Schapira, UCL Institute of Neurology, UK

Ferman TJ, Boeve BF, Smith GE *et al.*
Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology* 77(9), 875–882 (2011).

Dementia with Lewy-bodies (DLB) together with vascular dementia is the second most common type of dementia after Alzheimer's disease. The first international consensus criteria (ICC) for a clinical diagnosis of DLB had low sensitivity, suggesting that DLB was underdiagnosed. Patients with DLB have a more impaired quality of life, higher costs and a higher risk of adverse events to antipsychotic drugs than those diagnosed with Alzheimer's disease. Thus, adequate diagnosis is important and has clinical consequences. The revised criteria in 2005 included three suggestive features to increase diagnostic accuracy: severe neuroleptic sensitivity, pathological dopamine transporter scanning, and rapid eye movement sleep behavioral disorder (RBD). These criteria have not yet been adequately validated, although preliminary evidence suggests that they are more sensitive than the previous criteria.

The study by Ferman *et al.* analyzed the autopsies of 234 dementia patients who underwent annual assessments until death. The comprehensive assessment program was based on standardized instruments, including a clinical diagnosis of RBD using the validated Mayo Sleep Questionnaire, and overnight polysomnography was carried out

when possible. RBD occurred in 74 out of 98 patients in the DLB group, and preceded the estimated onset of dementia with 6 years. Patients with a history of RBD were six-times more likely to have autopsy-confirmed DLB. The sensitivity and specificity of the revised ICC for a pathological diagnosis of DLB were 85 and 73%, respectively. When RBD was added, there was a significant improvement in the regression model, sensitivity increased to 88% without reducing specificity. This study shows that DLB can be accurately diagnosed using the ICC, and that RBD adds to the diagnostic sensitivity.

– Article suggested and written by
Dag Aarsland

Ioannidis JP, Panagiotou OA.
Comparison of effect sizes associated with biomarkers reported in highly cited individual articles and in subsequent meta-analyses. *JAMA* 305(21), 2200–2210 (2011).

Most scientists would agree that positive results are more likely to get published and cited compared with negative results. This may give a false impression regarding the current state of research. In a recent paper, Ioannidis and Panagiotou set out to determine the magnitude of this problem in biomarker research. They examined biomarker articles cited more than 400 times in ISI Web of Science throughout 2010 and compared the effects reported in 35 eligible

News & Views

News

Journal Watch

Ask the Experts

Conference Scene

future
medicine part of fsg

studies against results of meta-analyses and larger studies on the same biomarker. For 30 of the 35 frequently cited biomarkers, the largest study of each marker reported less promising effects than those reported in the highly cited study. In 29 of the 35 cases, smaller effect sizes were reported in the meta-analyses. The authors conclude that highly cited biomarker studies often overestimate the findings and caution against rapid clinical adoption in the absence of evidence from multiple large investigations and meta-analyses.

– Article suggested and written by
Henrik Zetterberg

Yaffe K, Laffan AM, Harrison SL *et al.* Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 306(6), 613–619 (2011).

Mounting evidence suggests that cerebral hypoxia may play a role in the pathogenesis of a number of dementing illnesses, including Alzheimer's disease. One of the most common causes of cerebral hypoxia is sleep apnea, a category of sleep-disordered breathing, with an estimated prevalence among the elderly of 60%. In a longitudinal sample of 298 elderly women, Yaffe and colleagues related baseline measures of apnea, hypoxia, sleep fragmentation and sleep duration to future cognitive decline during 5 years of follow-up. After adjusting for demographic and physiological factors, the researchers found that the odds of developing cognitive impairment or dementia were 85% higher for women with biomarker evidence of sleep-disordered breathing compared with those without. This association was primarily driven by measures of hypoxia. Since no medications are currently available to prevent the progression of mild cognitive impairment to dementia, it might be worthwhile to screen at-risk individuals for sleep-disordered breathing and examine continuous positive airway pressure treatment as a possible prevention strategy against cognitive decline.

– Article suggested and written by
Henrik Zetterberg

Rascol O, Fitzner-Attas CJ, Hauser R *et al.* A double-blind, delayed-start trial of rasagiline in Parkinson's disease (the ADAGIO study): prespecified and *post hoc* analyses of the need for additional therapies, changes in UPDRS scores, and nonmotor outcomes. *Lancet Neurol.* 10(5), 415–423 (2011).

Dopaminergic therapies have been an important development for those suffering with Parkinson's disease (PD). However, patients continue to deteriorate over time and disabilities continue owing to features that are not fully controlled with dopaminergic treatment. Finding a drug that can reduce disease progression and thus, delay the onset of disability is a critical goal. The multicentre Attenuation of Disease Progression With Azilect Given Once-Daily (ADAGIO) study utilized a delayed-start design to investigate whether rasagiline, a selective, irreversible, second-generation monoamine oxidase-B inhibitor used for symptomatic treatment of PD, may also have a disease-modifying effect. The primary analysis published in 2009 demonstrated that for early-stage PD patients, a 1 mg dose of rasagiline met all three clinical end points for disease modification, whereas a 2 mg dosage met only two of the three primary end points. In this follow-up paper, the authors reported additional secondary and *post hoc* analyses of the ADAGIO study; namely analyses of the need for additional dopaminergic treatment, the contributions of different UPDRS subscores to treatment effects and the effect on nonmotor symptoms.

The authors found that rasagiline 1 mg and 2 mg delayed the need for additional antiparkinsonian therapy. At week 36 (delayed start of rasagiline) both doses significantly improved UPDRS motor subscores compared with placebo, and activities of daily living (ADL) subscores. At week 72 of the trial, ADL was the only subscore exhibiting a statistically significant between-group difference at 1 mg per day. Upon investigation of the effect on nonmotor symptoms at week 36, both doses produced benefits on the Parkinson fatigue scale versus placebo and the 1 mg

dose showed benefits on the scale for non-motor experiences of daily living compared with placebo. The rate of progression of total UPDRS score correlated with baseline severity and was less than anticipated from previous studies; for patients in the placebo group the UPDRS was 4.3 points over 36 weeks (approximately six units per year).

Overall the findings demonstrate that rasagiline can delay the requirement for symptomatic antiparkinsonian drugs, and underscore the contribution of the UPDRS ADL subscore in the response of the rasagiline 1 mg per day early-start versus delayed-start group. The authors conclude that further understanding of the pattern of UPDRS deterioration is essential in assessing disease modification.

– Written by Peter Livermore. Article suggested by Anthony Schapira

Weir DW, Sturrock A, Leavitt BR. Development of biomarkers for Huntington's disease. *Lancet Neurol.* 10(6), 573–590 (2011).

There are no currently available disease-modifying treatments for Huntington's disease (HD). However, following on from the discovery of the mutation of *HTT* responsible for HD, important advances have been made toward our understanding of the clinical, genetic, pathological and biochemical aspects of this disease. Therefore, a promising opportunity exists: the potential to prevent the onset of clinical manifestations by treating premanifest mutation carriers. For these individuals, predictive genetic testing could provide a window of opportunity for intervention aimed at preventing or delaying disease onset. However, in order for the efficacy of the therapeutic interventions to be assessed in this premanifest HD population, we require reliable and practical measures of disease progression (i.e., biomarkers). In this paper, Weir *et al.* review current progress in the development of biomarkers that might enable evaluation of disease progression in individuals at the premanifest stage of the disease and define

end points in clinical trials in this population. The authors review clinical, cognitive, neuroimaging and biochemical biomarkers that are currently being investigated for their potential clinical use and utility in the development of future therapeutics for HD patients. They conclude that before this potential can be realized, rigorous and well designed longitudinal studies are required to validate any of these putative biomarkers. In addition, as the field progresses with biomarker research, the

authors recommend that we should be cautious where ethical concerns may arise. As an example, they cite the situation of using measurements that might purposefully or unwittingly transgress established counseling protocols aimed at preparing individuals for the resultant psychological effects of a positive Huntington's disease genetic test.

– Written by Peter Livermore. Article suggested by Anthony Schapira

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Journal Watch highlights some of the most important papers recently published in the field of neurodegenerative disease management and research. The editorial team welcomes recommendations for relevant papers for inclusion in future issues.

Please direct your suggestions to:
Peter Livermore, Commissioning Editor
p.livermore@futuremedicine.com