JOURNAL WATCH

Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of *Clinical Practice*

Expert panel: Michael Berk, Lesley Berk, Alba A Brandes, Marco Bartolotti, Preethi Yerram, Adam Whaley-Connell, Robert S Dieter, Aravinda Nanjundappa, Joseph H Friedman, Josh Nadeau, Eric A Storch, Maria Vella & Dudley Robinson

Schneider MR, Delbello MP, McNamara RK, Strakowski SM, Adler CM. Neuroprogression in bipolar disorder. *Bipolar Disord.* 14(4), 356–374 (2012).

On aggregate, in people with bipolar disorder, and in other disorders including major depressive disorder and schizophrenia, a constellation of illness characteristics are consistent with those of a neuroprogressive illness [1]. Such evidence includes poorer symptomatic, treatment and functional outcomes in those with early onset and an increased number and length of episodes of illness, where longer and more frequent episodes catalyze vulnerability for further episodes. A declining probability of response to treatment and functional decline are similarly described with progression of the disorder. Pathophysiological evidence from biochemical and neuroimaging studies provide some support for this model. Concordant with approaches pioneered in oncology and cardiovascular disease, notions of staging are just beginning to inform therapeutic approaches. This paper by Schneider *et al.* reviews the evidence supporting the neuroprogressive processes in bipolar disorder, including neurocognition and structural brain changes. Both neurodevelopmental and neurodegenerative processes may play a role in the evolution of the process of neuroprogression. There are a number of potential molecular mechanisms that underpin this process, including the role of neurotransmitter systems, neurotrophins and regulation of neurogenesis, inflammatory, oxidative and nitrosative stress pathways, cortisol and the hypothalamic–pituitary–adrenal axis modulation, mitochondrial dysfunction and epigenetic factors [2,3]. The authors primarily examined the neuroimaging database, and found an emerging evidence base suggesting there are both developmental influences as well as evidence of a progressive neurophysiological process that is active in bipolar disorder. Due to methodological issues, and the paucity of quality data, especially prospective studies, they argue that the interpretation of correlations between neuroimaging findings and clinical measures should be performed with care. Nevertheless, the construct of neuroprogression dovetails with the staging model, and lends empirical support to the concept of early intervention, and the promise of neuroprotection.

– Written by Michael Berk & Lesley Berk

References

1 Moylan S, Maes M, Wray NR, Berk M. The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol. Psychiatry* doi:10.1038/mp.2012.33 (2012) (Epub ahead of print).

2 Maes M, Fišar Z, Medina M, Scapagnini G, Nowak G, Berk M. New drug targets in depression: inflammatory, cell-mediated immune, oxidative and nitrosative stress, mitochondrial, antioxidant, and neuroprogressive pathways. And new drug candidates – Nrf2 activators and GSK-3 inhibitors. *Inflammopharmacology* 20(3), 127–150 (2012).

3 Grande I, Magalhães PV, Kunz M, Vieta E, Kapczinski F. Mediators of allostasis and systemic toxicity in bipolar disorder. *Physiol. Behav.* 106(1), 46–50 (2012).

Future Medicine part of fsg

Wick W, Platten M, Meisner C *et al.* Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, Phase 3 trial. *Lancet Oncol.* 13(7), 707–715 (2012).

In this Phase III randomized trial the authors compared radiotherapy, which is the standard treatment for elderly patients (age >65 years) with high grade gliomas, with dose-dense temozolomide. In the trial, 373 patients were randomized to receive radiotherapy (60 Gy in 30 fractions of 1.8–2.0 Gy) or temozolomide 100 mg/m^2 on days 1–7 of 1 week on, 1 week off cycles. The primary end point was to prove the noninferiority of temozolomide versus radiotherapy in terms of overall survival (OS). Median OS was 8.6 months in the temozolomide group versus 9.6 months in the radiotherapy group (hazard ratio: 1.09; p[non-inferiority] = 0.033). *MGMT* methylation was found in 73 (35%) of the 209 patients tested. Patients with *MGMT* methylated had longer OS than those with *MGMT* unmethylated (11.9 vs 8.2 months; hazard ratio: 0.62; p = 0.014) and longer event-free survival (5.7 vs 3.5 months; hazard ratio: 0.50; p < 0.0001). Event-free survival was longer in patients with *MGMT* methylation who received temozolomide than in those who underwent radiotherapy (8.4 vs 4.6 months), whereas the opposite was found in unmethylated patients (3.3 vs 4.6 months). A similar, but nonsignificant effect was seen for OS.

The study demonstrated that temozolomide is noninferior to radiotherapy in the treatment of elderly patients and that *MGMT* is a useful predictive biomarker for outcome that could help clinicians to choose the best treatment for this subset of patients.

– Written by Alba A Brandes & Marco Bartolotti

Inker LA, Schmid CH, Tighiouart H *et al.* Estimating glomerular filtration rate from serum creatinine and cystatin C. *N. Engl. J. Med.* 367, 20–29 (2012).

In this study, the authors used cross-sectional analyses from 13 studies involving 5352 patients to develop estimating equations based on cystatin C by itself and in combination with creatinine, which were then validated in 1119 participants from five different studies in which glomerular filtration rate (GFR) was measured. The authors noted that the creatinine–cystatin C equation was able to estimate GFR closer to the measured GFR than equations that used creatinine or cystatin C alone. The combined equation was able to more accurately classify patients as either less than 60 ml/min/1.73 m^2 or greater than or equal to 60 ml/min/1.73 m^2 in those with creatinine-based estimated GFR of 45–74 ml/min/1.73 m^2. The authors concluded that the combined cystatin C and creatinine-based equation is more accurate in estimating GFR compared to the equations based on either marker alone.

– Written by Preethi Yerram & Adam Whaley-Connell

Piccini JP, White JA, Mehta RH *et al.* Sustained ventricular tachycardia and ventricular fibrillation complicating non-ST-segment-elevation acute coronary syndromes. *Circulation* 126, 41–49 (2012).

In this study the authors analyzed over 9000 patients from a large glycoprotein IIb/IIIa trial in non-ST elevation acute coronary syndrome patients. The primary goal was to determine the incidence of ventricular tachycardia/ventricular fibrillation (VT/VF), its timing, as well as outcomes. Their data suggested that approximately 1.5% of patients had VT/VF and they were evenly divided between early (<48 h) and late (>48 h) from their presentation. Regardless of the timing, VT/VF portended a worse prognosis. This study highlights three major points: first, the incidence of VT/VF is less than what was previously thought in this patient population; second, VT/VF was evenly distributed between early and late presentation (as opposed to the ST elevation myocardial infarction patient where 90% of VT/VF is within the first 48 h); and third, regardless of the timing of VT/VF, these patients did worse than those without VT/VF.

– Written by Robert S Dieter & Aravinda Nanjundappa

Hardy J, Revesz T. The spread of neurodegenerative disease. *N. Engl. J. Med.* 366, 2126–2128 (2012).

This extremely brief piece brings to the general medical press a new and exciting concept that may help explain how neurodegenerative disorders disseminate within the brain. There is a generally accepted staging system for both Alzheimer's and Parkinson's disease, the most common of the neurodegenerations, in which the early stages are localized to particular regions before spreading. Animal work, sparked in part by the observation that experiments in humans, in which fetal cells were implanted into Parkinson's disease patients developed pathological changes of Parkinson's disease, shows that abnormally folded pertinent proteins may not only cause the neurofibrillary tangles of Alzheimer's disease in the cells they are in, but get transmitted downstream where they act as templates to produce further damage. In this regard they act like prions, although they are not. These observations should lead to better animal models and new approaches to halting progression. They may also explain why these disorders are usually asymmetric.

– Written by Joseph H Friedman

Roessner V, Schoenefeld K, Buse J, Bender S, Ehrlich S, Munchau A. Pharmacological treatment of tic disorders and Tourette Syndrome. *Neuropharmacology* doi:10.1016/j.neuropharm.2012.05.043 (2012) (Epub ahead of print).

Roessner and colleagues reviewed data on pharmacological treatments for tic disorders (e.g., Tourette syndrome), including typical and atypical antipsychotics, noradrenergic, benzamides and various alternatives. Surprisingly, relatively few large randomized controlled trials have been reported, limiting conclusive recommendations, especially in the presence of comorbidity. Given the extant empirical data, risperidone and tiapride were suggested as first-line pharmacological treatment options, while pimozide and aripiprazole were listed as second-line options. However, side effects – most notably extrapyramidal symptoms and cardiac and metabolic effects – are common, which limits medication acceptability and is frequently associated with attrition. Pharmacological treatment recommendations to address specific comorbid conditions are discussed, as response may be moderated by comorbidity presence. Overall, this article provides a comprehensive overview of pharmacological interventions for tic disorders, although it includes only a limited discussion of psychosocial approaches for tics (e.g., Comprehensive Behavioral Intervention for Tics) or commonly comorbid conditions (e.g., cognitive–behavioral therapy). As noted, there is a clear need for additional trials with heterogeneous patient samples that allow for the examination of treatment response and outcome moderators.

– Written by Josh Nadeau & Eric A Storch

Cardozo L, Hall T, Ryan J *et al.* Safety and efficacy of flexible-dose fesoterodine in British subjects with overactive bladder: insights into factors associated with dose escalation. *Int. Urogynecol. J.* doi:10.1007/s00192-012-1804-1 (2012) (Epub ahead of print).

Antimuscarinics are currently the mainstay of treatment for women with an overactive bladder although patient compliance is generally limited by their efficacy to tolerability ratio. Flexible dosing enables titration to symptoms and side effects, thus allowing individualization of treatment. There is currently very little understanding of methods of identification of patients who will benefit from dose escalation.

Fesoterodine is an antimuscarinic available in 4 mg and 8 mg doses. A recent 12-week multicenter open-label study was carried out to evaluate its safety and efficacy and the factors involved with dose escalation in subjects with overactive bladder. Overall, 331 patients were recruited.

They all complained of overactive bladder symptoms and were all treated with 4 mg fesoterodine. After 4 weeks they were given the option of escalating to the 8 mg dose. A decision was made following a discussion with the patient regarding their experience of efficacy and tolerability. Factors influencing dose escalation included patient-reported outcomes, using the patient perception of bladder condition questionnaire and variables from a 3-day bladder diary. A stepwise logistic regression analysis was carried out.

Of the patients, 195 (59%) dose escalated at 4 weeks. This subgroup showed less improvement in bladder diary variables and patient perception of bladder condition questionnaire at 4 weeks than nonescalators. By week 12 the two groups showed similar improvement levels and fesoterodine was well tolerated by all subjects. Patients who showed less improvement were more likely to want to dose escalate.

The information from this study may help clinicians to tailor antimuscarinic treatment for individual patients and this may lead to an improvement in compliance and persistence.

– Written by Maria Vella & Dudley Robinson

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