Treatment Response and Redefining Diagnostic Boundaries

By Eric Hollander, MD

This issue of *CNS Spectrums* attempts to help translate research developments into new treatments, into everyday clinical practice, and into defining the boundaries of broader diagnostic categories.

Obsessive-compulsive spectrum disorders (OCSDs) are more common in patients with rheumatic fever (RF). André Augusto Anderson Seixas, MD, and colleagues determined whether RF or Sydenham's chorea increases the probability of anxiety disorders in first-degree relatives of individuals with RF with and without Sydenham's chorea in 98 probands and 389 first-degree relatives. Generalized anxiety disorder (GAD) occurred more frequently in the first-degree relatives of RF probands than in those of control probands. The presence of RF, GAD, or separation anxiety disorder in one family member significantly increased the chance of OCSDs in another member of the family.

There was familial aggregation among RF, GAD and OCSDs. Clinicians should be aware to the possible familial relationship between GAD and OCSD in their RF patients and their family members, which may suggest a genetic component between them. Further studies on obsessive-compulsive disorder (OCD) should include anxiety disorders to better define the OCD spectrum. This work is particularly timely in helping to determine where OCSDs should be placed in the forthcoming *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Part of this decision rests on whether OCD is closer, based on multiple validators (such as family history or immune factors), to other OCSDs or to other anxiety disorders. This type of work provides interesting data with regard to some of these validators, and thus helps determine how to cleave nature at its joints with regard to diagnostic boundaries.

Guanfacine is a noradrenergic agonist that may improve symptoms of attention-deficit/hyperactivity disorder (ADHD) via selective actions at α_{2A}-adrenoceptors in the prefrontal cortex. A recent controlled multicenter trial supports the efficacy and safety of guanfacine extended release for pediatric ADHD. Joseph Biederman, MD, and colleagues conducted a long-term, open-label extension to study the safety profile and effectiveness of guanfacine extended release for up to 2 years in 240 children and adolescents 6–17 years of age with a diagnosis of ADHD. The most common adverse events were somnolence, headache, fatigue, and sedation, which were usually transient. Cardiovascular-related adverse events were uncommon, although small reductions in mean blood pressure and pulse rate were evident at monthly visits. ADHD Rating Scale, Version IV total and subscale scores improved significantly from baseline to endpoint for all dose groups, and effectiveness was maintained over this 2-year period.

Mark K. Boschen, PhD, MAPS, conducted a prospective outcome study of two cohorts of patients with chronic, resistant OCD. One consisted of 52 patients treated in an inpatient setting, while the second comprised 65 patients treated in a community outpatient setting. Treatment involved intensive graded exposure and self-imposed response prevention augmented with cognitive restructuring. In both inpatient and community groups, there was significant improvement over the first 12 weeks of treatment, with further improvement between 12 and 24 weeks. Treatment-resistant patients benefited from intensive behavioral therapy of OCD, and for those with the most profound refractory OCD, inpatient stays of up to 24 weeks were effective in reducing symptoms. Unfortunately, such lengthy inpatient stays are not widely available in the United States due to insur-

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ance reimbursement limitations. Nevertheless, this study provides hope for resistant and refractory OCD populations if access to intensive exposure-response prevention is available.

Selective serotonin reuptake inhibitors are first-line pharmacologic options for the treatment of depression. However, only 50% to 70% of patients respond to initial treatment and <40% remit. Since depression is associated with substantial morbidity, mortality, and family burden, it is unfortunate and demanding on health resources that patients must remain on their prescribed medications for at least 4 weeks without knowing whether the particular antidepressant will be effective. Studies have suggested a number of predictors of treatment response, including clinical, psychophysiological, neuroimaging, and genetics—each with varying degrees of success and nearly all with poor prognostic sensitivity and specificity. Studies are yet to be conducted that use multiple measures from these different domains to determine whether sensitivity and specificity can be improved to predict individual treatment response. Andrew H. Kemp, PhD, and colleagues propose the use of standardized testing methods across multiple modalities and their integration in order to translate research findings into clinical practice. Again, this is an important gap in our knowledge between individual research findings of response predictors, and the limited practical use of treatment predictors in clinical practice. Ultimately, translational approaches include not only translating fundamental basic science developments into breakthrough new treatments but also translating clinical research findings into efficient changes in clinical practice to maximize functional outcomes.

The articles in this issue, the last of 2008, have highlighted some attempts to translate research developments into new treatments, into everyday clinical practices, and into defining the boundaries of broader diagnostic categories. The familial aggregation of RF with both OCSDs and GAD has implications for *DSM-V* diagnostic boundaries. Intensive exposure and response prevention strategies seem to help treatment-resistant and refractory OCD, but access to such treatments may be limited. The use of multimodal predictors may eventually help improve the accuracy of predicting selective serotonin reuptake inhibitor response in depression. Finally, noradrenergic modulators seem to help ADHD symptoms over extended periods of time.

In closing, I would like to wish our readers happy holidays. ***CNS***

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