Tramiprosate Falls Short in Phase III Alzheimer’s Trial

Unusually large placebo effect could be a recurring problem in studies that allow concomitant medications.

**By Michele G. Sullivan**
Mid-Atlantic Bureau

The lack of diagnostic criteria has hamstrung attempts to diagnose involuntary emotional expression disorder. Dr. Sharon Handel said at a meeting on Alzheimer’s disease and related disorders sponsored by Johns Hopkins University.

Even when they make the diagnosis with certainty, physicians have little to offer by way of Food and Drug Administration-approved therapy, she said. Handel, of the department of psychiatry and behavioral sciences at Johns Hopkins University, Baltimore. Part of the problem with identifying this condition has been the numerous names under which it is known, she noted.

Involuntary emotional expression disorder (IEED) is also known as pseudobulbar affect and pathologic laughing or crying.

It’s estimated that more than 1 million people in the United States have IEED. The disorder has been associated with cerebrovascular accident, Alzheimer’s disease, multiple sclerosis, atypical lateral sclerosis, and traumatic brain injury.

The hallmark of IEED is episodes of crying or laughing that are unrelated to or out of proportion with the eliciting stimulus. There is a disconnection between emotional experience and expression. Emotional outbursts in IEED are involuntary, episodic, and incongruent with baseline mood. The outbursts are intense, but are followed by a return to baseline.

Disorders of affect—which IEED appears to be—involve impairment of the moment-to-moment regulation of emotion. “There’s a disconnection of the neural networks in this condition from the experienced emotion to the display of emotion,” Handel said.

The neural networks of emotion involve the frontal lobes, the limbic system, the brainstem, the cerebellum, and white-matter tracts. In particular, the prefrontal cortex integrates complex sensory and limbic information that determines the emotional valance of a stimulus and provides complete motor and autonomic responses involved in emotional expression. It’s not clear where the neural interruption occurs in IEED.

For now, the current diagnostic criteria include:

- Origin in brain injury or disease.
- A change in the patient’s emotional behavior from that prior to the disease or injury.
- Incongruent or exaggerated mood.
- A response that is excessive or unrelated to the stimulus.
- Significant distress or impairment.

The differential diagnosis should include epilepsy; facial dystonia or dyskinesias; vocal tics; axis I disorders (such as major depression or bipolar disorder); axis II disorders (such as borderline personality disorder); and substance abuse.

The differential diagnosis should also include affective liability, essential crying, and witzelsucht. With affective liability, the subjective and objective effects of the disorder are not dissociated. Essential crying is a hereditary and lifelong tendency to cry easily. Witzelsucht is an addiction to trivial joking, which can take the form of an inappropriate giddily affective or irritability or aggressiveness.

In terms of clinical course, IEED frequently remits spontaneously within 6 months. Others may have remission with treatment within 3 months. Resolution of IEED can be independent of the resolution of depression. However, in some cases the disorder is chronic and persistent without treatment.

Treatment of IEED is still evolving. At present, there is no FDA-approved treatment for IEED. “What are typically used—at least up to this point—are SSRIs. They tend to work quite quickly,” said Dr. Handel, who has no disclosures.

Dextromethorphan, in combination with quinidine, is being studied to treat patients who have IEED. Dextromethorphan is a nonopioid antinauseative, but it also has a number of other neuropharmacological properties. It is a potent inhibitor of this isomerase, thereby increasing and sustaining dextromethorphan levels.

IEED: Uncertainty Reigns In Diagnosis and Treatment

**By Kerri Wachten**
Senior Writer

BALTIMORE — The lack of diagnostic criteria has hamstrung attempts to diagnose involuntary emotional expression disorder. Dr. Sharon Handel said at a meeting on Alzheimer’s disease and related disorders sponsored by Johns Hopkins University.

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