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File: ■ Sceletium (*Sceletium tortuosum*)
■ Zembrin®
■ Anxiety

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RE: Anxiolytic Activity of Zembrin® Sceletium Extract in Humans

Terburg D, Syal S, Rosenberger LA, et al. Acute effects of *Sceletium tortuosum* (Zembrin), a dual 5-HT reuptake and PDE4 inhibitor, in the human amygdala and its connection to the hypothalamus. *Neuropsychopharmacology*. August 2013; [epub ahead of print]. doi: 10.1038/npp.2013.183.

Sceletium (*Sceletium tortuosum*) is a plant indigenous to South Africa with psychotropic (mood-altering) properties. Preliminary studies indicate that it may help anxiety and patients with depression. Sceletium works by inhibiting serotonin (5-hydroxytryptamine [5-HT]) reuptake transporters and selectively inhibiting phosphodiesterase-4 (PDE4) enzyme subtypes in the central nervous system (CNS). These actions may work synergistically. Certain conventional pharmaceuticals that treat anxiety and/or depression work on either the 5-HT transporter or PDE4 enzymes. The amygdala is an area of the brain involved in threat detection and regulates fear and anxiety. Researchers can assess acute anxiety by conducting functional magnetic resonance imaging (fMRI) of the brain to measure anxiety-related amygdala activation, and the subsequent connectivity of the amygdala with the cortical and/or subcortical threat circuit. Hence, the purpose of this small, double-blind, placebo-controlled, crossover study was to evaluate the acute anti-anxiety effects of a single dose of sceletium during amygdala neurocircuitry stimulation.

Healthy undergraduate students (n = 16; aged 18-21 years; equivalent genders) from the University of Cape Town (Cape Town, South Africa) who were right-handed, medication-free, had no history of neurological disease or psychopathology, and had normal or corrected-to-normal vision were included in the study. Subjects received either sceletium (25 mg Zembrin®; HG&H Pharmaceuticals; Bryanston, South Africa) or placebo 2 hours prior to undergoing the fMRI scan. Zembrin is a standardized extract of the aerial plant parts of sceletium extracted with 70% ethanol and then spray-dried onto maltodextrin and contains the 4 active alkaloids – mesembrenone, mesembrenol, mesembranol, and mesembrine. Each tablet contains the equivalent of material derived from 50 mg of the dried aboveground plant. There was a 5- to 9-day washout between treatments for each subject. During the scan, subjects performed the 2 following tasks: the perceptual-load task (PLT) and the emotion-matching task (EMT). The PLT

assesses state anxiety-related amygdala activity (the subjects identify letters on faces that are either neutral or with a fearful expression to induce anxiety). The EMT is a reliable amygdala activator (subjects match either ovals or faces expressing anger or fear); it is used to assess amygdala-hypothalamus coupling.

During the PLT, amygdala reactivity to facial fear under low-load conditions was significantly reduced after sceletium administration compared with placebo ($P = 0.020$). As expected, the EMT showed activation of the midbrain, hypothalamus, amygdala, and ventromedial prefrontal cortex/orbitofrontal cortex (vmPFC/OFC). During the EMT, there was a significant decrease in functional connectivity between the amygdala and the hypothalamus after sceletium administration compared with placebo ($P = 0.034$). The connectivity between the amygdala and the midbrain or vmPFC/OFC was not affected by sceletium treatment. No general subjective mood effects were observed.

The authors conclude that Zembrin compared with placebo administration reduces anxiety-related amygdala reactivity and decreases amygdala-hypothalamus coupling in the subcortical threat circuit. Although there were no general subjective mood effects, the authors state that the effects reflect a reduction of responsivity of the threat system related to the anxiolytic properties of sceletium. These results help support the neurological mechanism of action of sceletium and provide further rationale for exploring potential therapeutic efficacy in future clinical trials.

—Heather S. Oliff, PhD

Referenced article can be found at http://www.nature.com/npp/journal/vaop/ncurrent/full/npp2013183a.html.