POSTER ABSTRACTS

New Approaches to Mental Illness

in the Era of the National Brain Initiative

ASCP Annual Meeting

June 16 - 19, 2014

Hollywood, FL

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Michael R. Liebowitz, Louis Monti, Rita Hanover, Bernard Grosser. A Rapidly Acting Intranasal Treatment for the Symptoms of GAD. ASCP Annual Meeting: New Approaches to Mental Illness in the Era of the National Brain Initiative. June 16-19, 2014. Hollywood, Florida.

Background. Although generalized anxiety disorder (GAD) is a common and sometimes disabling condition, there is a need for additional treatments other than benzodiazepines that can be used on a prn basis to help with the severe anxiety and distress that many affected individuals experience.

PH94B is a new investigational drug for the acute treatment of Social Anxiety Disorder. Chemically, PH94B is an odorless, neuroactive steroid compound with proven lack of affinity to steroidal hormone receptors. It is thought to act via nasal chemosensory receptors that broadcast chemosensory information to specific brain areas (cingulate gyrus, hypothalamus, limbic amygdala, anterior gyrus and prefrontal cortex) which are different from the brain areas activated by olfactory stimuli.

Earlier studies demonstrated that picomol quantities of PH94B induced dose-dependent membrane currents and increased Ca_i^{2+} in isolated human nasal chemosensory cells, and depolarization of the human nasal chemosensory epithelium, followed by small but significant decreases in heart rate, respiratory rate, electrodermal activity, and blinking reflex, and increased alpha-EEG and body temperature. A number of the volunteers spontaneously reported feeling distinctly calm and less nervous during these studies. Similar results were obtained in a Phase I dose escalation study.

Methods. To continue this exploration of PH94B, 28 patients with GAD (DSM-IV) were enrolled in a randomized, placebo-controlled, double blind study. Following exclusion of placebo responders (n = 7) 21 patients were randomized to receive 200 pg PH94B or placebo in a one second aerosol pulse to the chemosensory epithelium of the anterior nasal septum. HAM-A, and clinical electrophysiological measures were administered at randomization (Baseline) and 30 and 60 min

following treatment. Because of the small sample size and lack of power, effect sizes (Cohen's d) were evaluated in addition to between-group comparisons.

Results. Nineteen completed the study (2 early terminators). Thirty minutes after treatment there was mean reduction of 32.0% (8.7 points) for the PH94B group (n = 11) and 19.6% (5.1 points)for the Placebo group (n = 8) in total HAM-A ($p = 0.09$, one-tail t-test; Cohen's $d = 0.644$) Electrophysiological changes (respiratory, cardiac, and electrodermal frequency), concordant with the reduction in anxiety, were significantly greater for the PH94B group ($p's < 0.003$, one-tail; Cohen's d range: 1.3 to 8.0).

Further exploration of group differences for individual HAM-A item scores revealed impressive effect sizes for improvement in Anxious Mood Cognition Depressed Mood Cardiovascular Symptoms and Other Autonomic Symptoms Cohen's d range: from 0.469 to 1.59).

After 60 min, all significant improvements and group differences had disappeared.

Conclusions.

PH94B may be useful as a prn treatment for GAD, although further trials with larger samples are indicated.

PH94B may be useful in other anxiety states where rapid, temporary relief would be of benefit, like performance and social anxiety that is part of social anxiety disorder. In fact, this was recently demonstrated in a placebo controlled trial.

Nasal chemosensory cells may be a portal of entry for substances affecting feeling states.

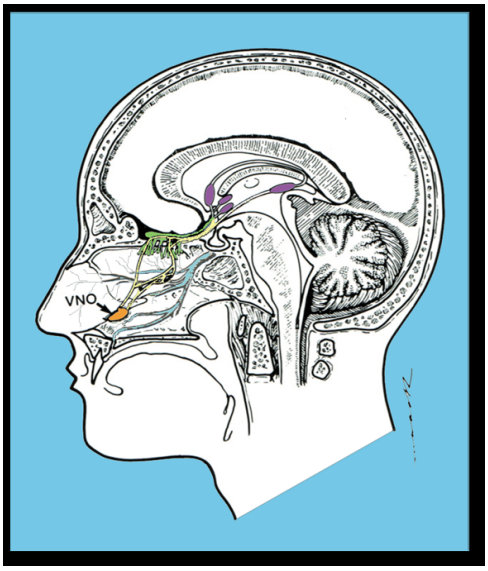

Figure 1. Human Nasal Chemosensory Systems

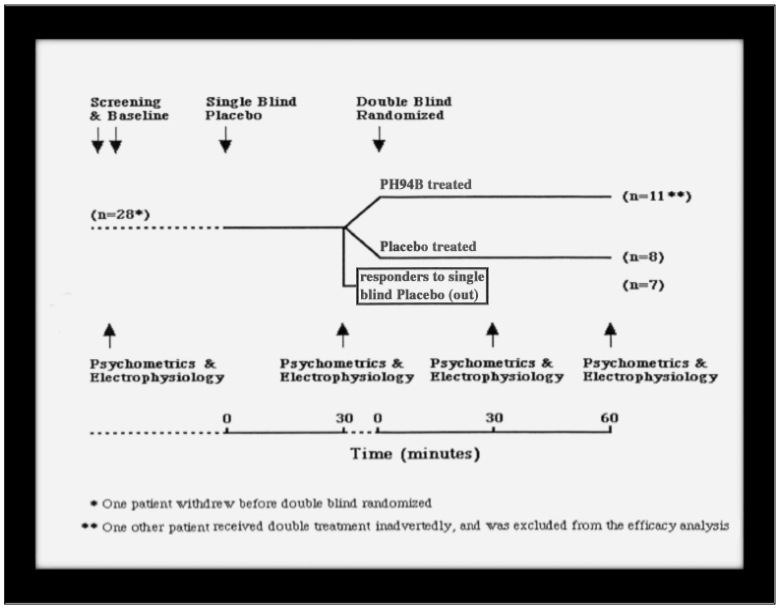

Figure 2. PH94B in GAD Patients: Acute Challenge

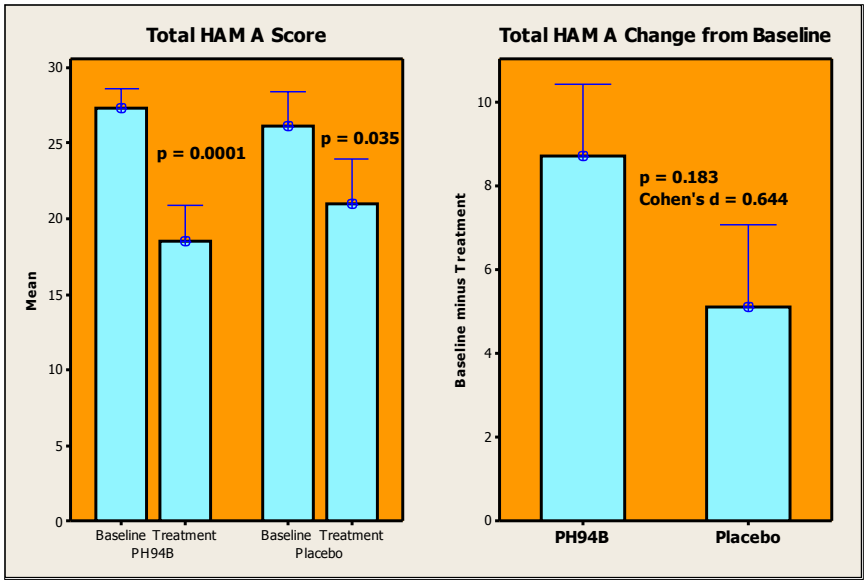

Figure 3. Total Hamilton-A Scores Change from Baseline to 30-minutes with PH94B vs. Placebo

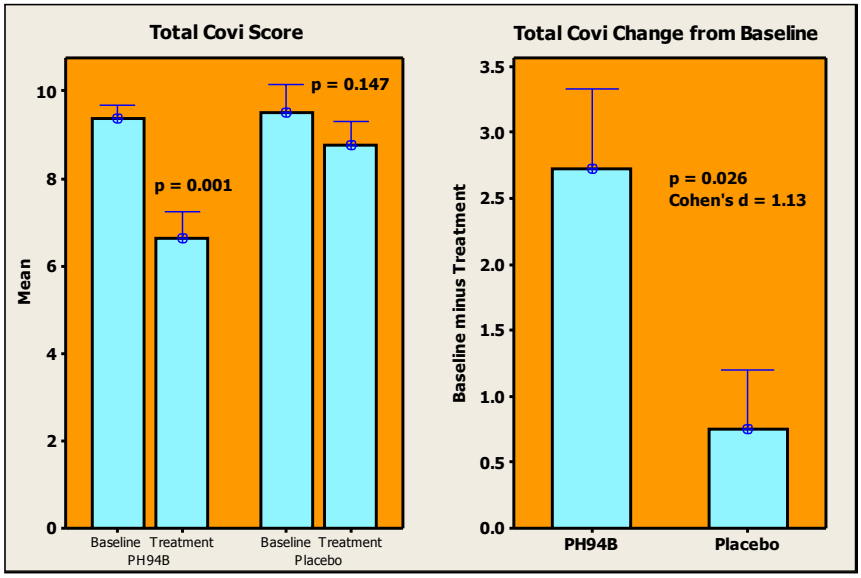

Figure 4.Total Covi Scores Change from Baseline to 30-minutes with PH94B vs. Placebo

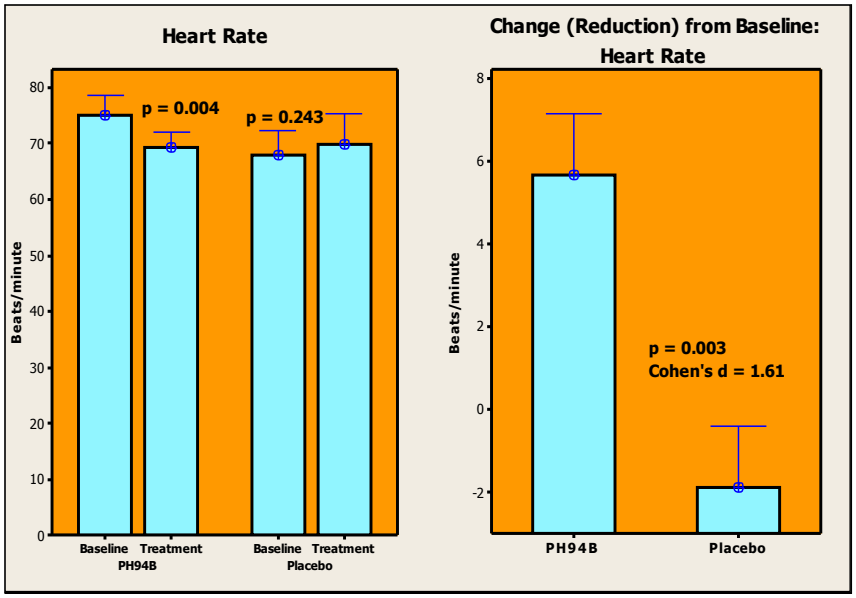

Figure 5. Heart Rate Change from Baseline to 30-minutes with PH94B vs. Placebo

HAM A Item	Effect Size		Physiologic Measure	Effect Size
Concentration/Memory	1.59		Electrodermal Activity	8.01
Anxious Mood	0.927			
Other Autonomic Symptoms	0.796		Heart Rate	1.61
Depressed Mood	0.686			
Cardiovascular Symptoms	0.469		Respiration Rate	1.3
Somatic, Muscular	0.215			
Gastrointestinal Symptoms	0.153		Body Temperature	1.04
Tension	0.08			
Behavior at Interview	0.05		Electromyogram	0.783
Respiratory Symptoms	-0.07		-	-
Genitourinary Symptoms	-0.09		-	-
Somatic, Sensory	-0.31		-	-

Table 1. Effect sizes for Hamilton –A Items and Physiologic Measures: PH94B vs. Placebo

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