



Protagenic Therapeutics' Lead Candidate PT00114 Attenuated Chronic Stress Responses in a Well-Established Rodent Model

As published in Behavioural Pharmacology, two days of PT00114 treatment reduced corticosterone levels and attenuated anxiety-like behavior in chronically stressed rats; a known CRF₁ receptor antagonist did not show activity in the same model.

NEW YORK, NY / June 30, 2026 — Protagenic Therapeutics, Inc. (OTCQB: PTIX), a clinical-stage biopharmaceutical company focused on novel neuropeptide therapies for stress-related disorders, today announced the publication of new preclinical data for its lead candidate, PT00114, in the peer-reviewed journal *Behavioural Pharmacology*. In a well-established rodent model of chronic unpredictable stress, PT00114 reduced both physiological and behavioral markers of chronic stress after stress had been established, while the prototypical non-peptide corticotropin-releasing factor receptor 1 (CRF₁) antagonist CP-154,526 did not show activity on the same endpoints.

Why These Findings Matter

As part of their pre-clinical investigation program, using a 14-day chronic unpredictable stress paradigm in male Sprague Dawley rats, the researchers evaluated PT00114 against saline as a control and CP-154,526 as a comparator.

Key results:

- PT00114 reduced stress-induced plasma corticosterone by 56.4%, relative to stressed, saline-treated controls ($p = 0.029$), after two 250 nmol/kg doses administered subcutaneously on days 12 and 13 (11 days after initiation of chronic stress)
- PT00114 increased time spent in the center of an open field arena (a well-established experimental measure of reduced anxiety-related behavior) by 282% versus controls ($p = 0.031$). There was no significant change in total distance traveled—indicating that the effect was not attributable to a general change in locomotion.
- CP-154,526 did not affect either corticosterone or time spent in the center of the open field whether it was administered on days 12 and 13 or daily throughout the entire stress paradigm

These data provide further preclinical rationale for Protagenic Therapeutic's development strategy of evaluating PT00114 for the potential treatment of chronic, stress-related conditions. Protagenic has reported positive topline safety results from Phase 1 studies of PT00114 and plans to initiate subsequent clinical studies in 2027.

Translational Significance: Multiple, structurally distinct CRF₁ receptor antagonists have shown robust activity in acute-stress rodent models over the past two decades but have repeatedly failed to separate from placebo in clinical trials for generalized anxiety disorder (GAD), major depressive disorder, and related conditions. The study authors note that this preclinical-to-clinical gap has been attributed, in part, to an over-reliance on acute-stress models that may not reflect the sustained, heterogeneous nature of human anxiety and depression. In this study, PT00114 retained activity while a CRF₁ antagonist was ineffective in a chronic stress environment even with continuous dosing.

PT00114 is a synthetic analog of TCAP-1, a naturally occurring neuropeptide that helps regulate the CRF-mediated stress response, which may be dysregulated in chronic stress conditions such as GAD. Rather than competing with CRF at the CRF₁ receptor, PT00114 has the potential to act upstream of, or in parallel with, the CRF signaling cascade. The authors hypothesize that this broader, mechanistically distinct mode of action may be less susceptible to compensatory adaptations that are thought to limit the efficacy of CRF₁ antagonists under chronic conditions.

About PT00114 PT00114 is Protagenic’s lead clinical asset — a first-in-class investigational neuropeptide targeting the TCAP pathway for the treatment of stress-related neuropsychiatric disorders, including anxiety, PTSD, and treatment-resistant depression. PT00114 has completed single- and multiple-dose Phase 1 studies in healthy volunteers, where it was reported to be well tolerated.

About Protagenic Therapeutics, Inc. Protagenic Therapeutics, Inc. (OTCQB: PTIX) is a clinical-stage biopharmaceutical company dedicated to developing breakthrough peptide-based treatments for stress-related neuropsychiatric disorders. The Company is headquartered in New York, NY.

For more information, visit www.protagenic.com

Publication Details

Mueller LE, Siemian JN, Lovejoy DA, Stein RB, Slee AM. Teneurin C-terminal Associated Peptide-1 attenuates chronic stress in male rats. Behavioural Pharmacology. 2026. DOI: 10.1097/FBP.0000000000000886.

Forward-Looking Statements This press release contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, including but not limited to statements regarding the anticipated role and contribution of Dr. Floyd, the planned timing of Phase 2 enrollment for PT00114, and the therapeutic potential of PT00114. These statements are based on current expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results to differ materially from those expressed or implied. Protagenic Therapeutics undertakes no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law.

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