



HPA AXIS OPTIMIZATION PROGRAM

Supporting Hypothalamic-Pituitary-Adrenal
Axis Homeostasis

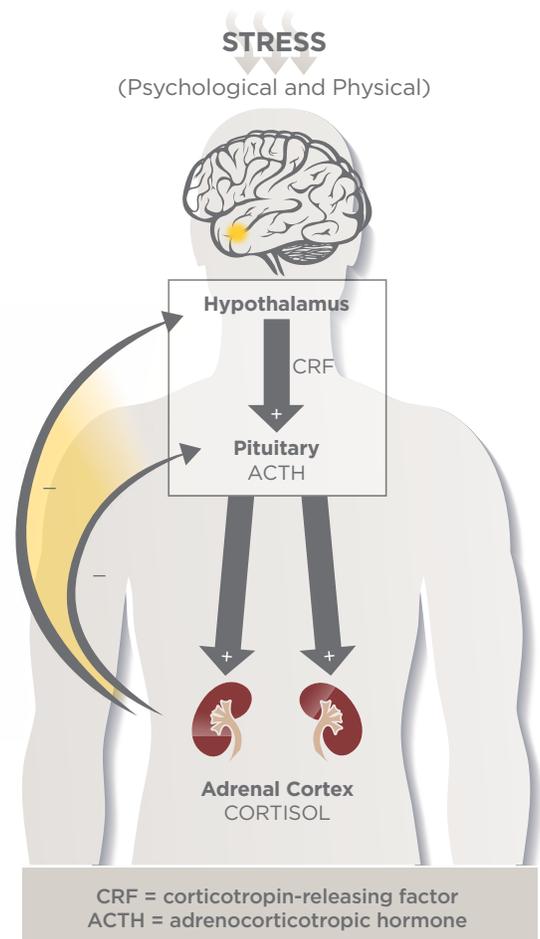


The Stress Progression

In a seminal paper published in 1950 in the *British Medical Journal*, Hans Selye MD, PhD, described the human physiological response to prolonged stress as a General Adaptation Syndrome (GAS).¹ Selye identified the three stages—alarm, resistance, and exhaustion—as a guide to assist healthcare professionals with their evaluation and early intervention strategies. While he illustrated the clinical utility of identifying these stages associated with GAS, he also cautioned, “The general adaptation syndrome never occurs in its pure form, but is always complicated by superimposed specific actions of the eliciting stressors.” The impact of stress is a spectrum requiring thorough practitioner analysis of each patient. And the impact of stress on what is now referred to as the hypothalamic-pituitary-adrenal (HPA) axis is individualized and varied in its outcome.

The HPA Axis

The HPA axis is a complex set of feedback interactions among the hypothalamus, the pituitary gland, and the adrenals. These interactions form a major part of the neuroendocrine system, which controls reactions to stress and regulates many body processes, such as digestion, immune function, mood and emotions, sexuality, and energy storage, and expenditure. The HPA axis is the uniting system for interactions of the glands, hormones, and parts of the brain that mediate the general adaptation syndrome.



The Stress Response

Stress can affect the function of metabolic processes regulated by the HPA axis. Although changes in metabolic function may at first be adaptive, on-going stress may necessitate additional support of various metabolic parameters. The HPA axis influences hormones, cytokines, glucose regulation, and other metabolic processes. Previously, clinicians focused on the necessity of supporting adrenal function and coined terms such as “adrenal fatigue;” however, we have since learned that the effects of stress affect more than the adrenals. In addition, focusing only on cortisol and/or adrenal function may overly simplify complex interactions among several systems, and miss the contributions of the central nervous system, environmental factors, and other metabolic factors.²

External stressors are translated into biochemical signals, many of which influence the feedback loops of the HPA axis. Prolonged stress may continually activate the HPA axis and affect the balance of hormone and cell mediators. Cortisol is perhaps the most important hormone involved in the adaption process. Cortisol is released by the adrenal cortex in response to stress; however, continued release affects hypothalamic and pituitary feedback loops³ in a way that may lead to persistent activation.

HPA axis activation and cortisol issues can persist for years, with effects on most major body systems including: gastrointestinal, neurological, musculoskeletal, endocrine, respiratory, and immune. Via the HPA axis, stress can affect physical, behavioral, and/or neuropsychiatric function.^{4,5}

The American Institute of Stress reports that 75–90 percent of visits to primary care physicians are stress-related; therefore, supporting HPA axis homeostasis is a significant clinical goal for a broad range of patients.⁶



Optimizing HPA Axis Function

The foundational strategy of HPA axis optimization involves effective detection of axis activation and attendant impact on cortisol, followed by an appropriately-designed lifestyle and dietary supplement regimen. The best opportunity for noticeable impact lies within the resistance stage of GAS, as presented by Selye. Modern understanding of HPA axis involvement in stress provides healthcare professionals with a unique opportunity to address underlying factors and help create a healthy stress response.

Integrative Therapeutics HPA Axis Optimization Program is designed to help healthcare professionals accurately assess common and complex symptoms within various stress response stages—thereby improving patients' ability to respond and adapt to stressful stimuli while promoting energy recovery and restorative sleep.

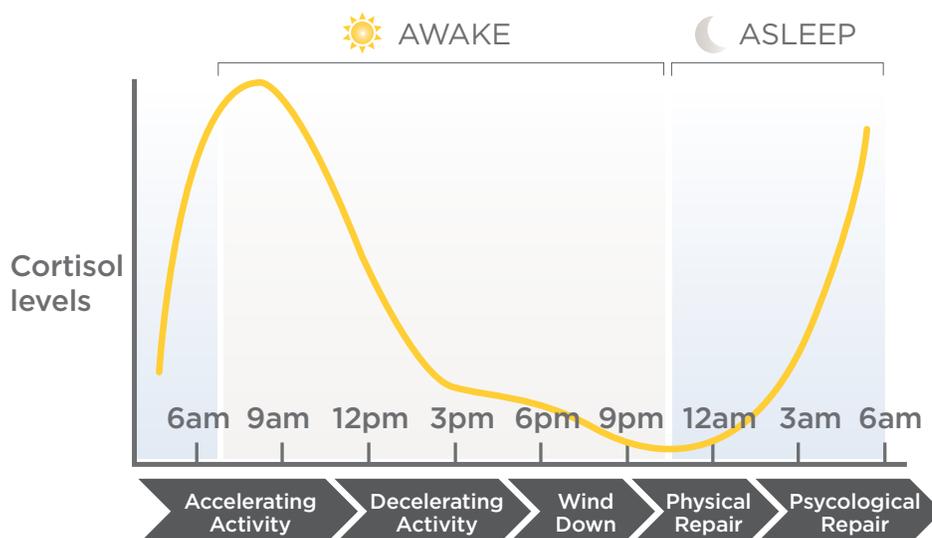
Along the entire stress spectrum, salivary cortisol monitoring is important, especially during the resistance stage. Glucocorticoids are significant regulators of physiological reactions to stress, and cortisol is the primary glucocorticoid that helps maintain homeostasis. Cortisol also stimulates the release of other hormones to maintain balance.

Balancing Cortisol

Under normal conditions, plasma cortisol peaks before awakening and decreases throughout the day. When cortisol levels are blunted upon awakening, this can indicate HPA axis disruption.⁷ Cortisol measurement throughout the day can provide valuable clinical information. Patients who are under stress may have surges of cortisol that are superimposed on the innate circadian patterns.⁸

HPA activation can also affect normal sleep cycles, and lack of sleep can alter HPA axis function and the glucocorticoid feedback loop.

Key clinical goals are to support hypothalamus and pituitary sensitivity to cortisol, maintain healthy circadian rhythm, and support limbic system activity to reduce inappropriate threat perception. Cortisol secretion should ideally peak between 6 AM and 8 AM, with a natural decline throughout the day and the lowest levels achieved between 6 PM and 8 PM.

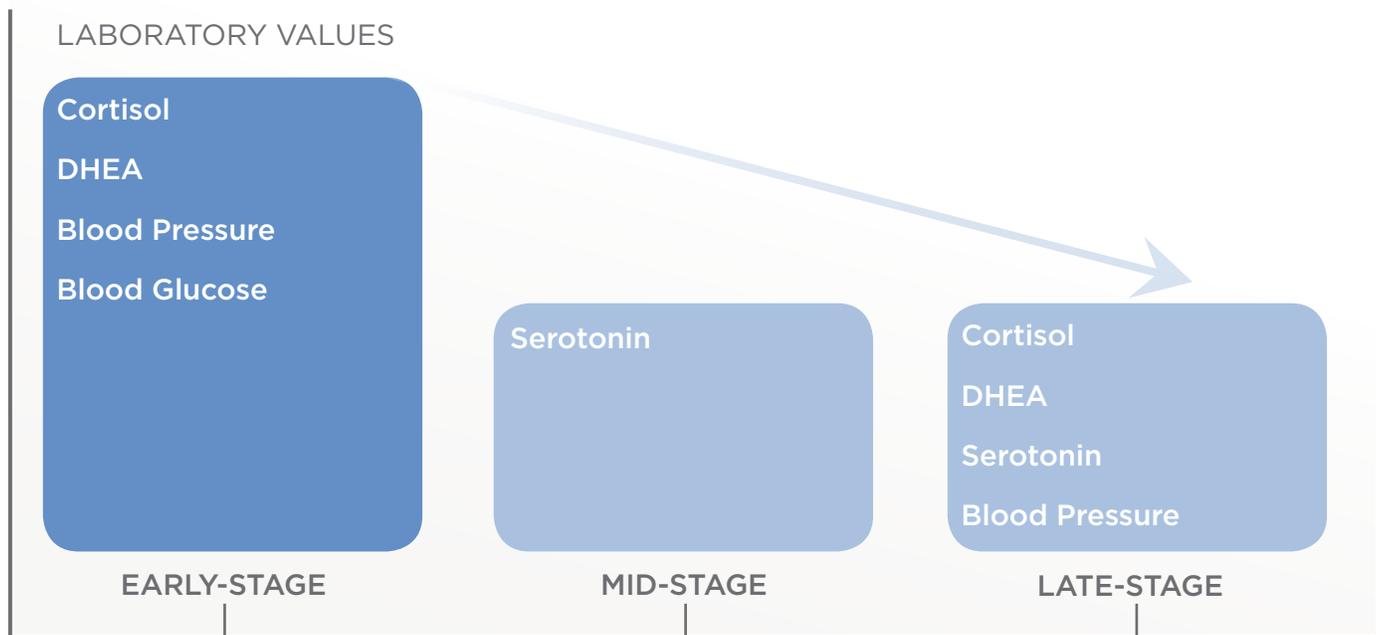


The Stress Presentation

The impact of stress is unique to each patient; it can manifest through a range of symptoms and laboratory values. Comprehensive practitioner analysis is necessary to identify the stress response stage and support each patient's unique needs.

The following chart provides a guideline for the spectrum of responses across the three Stages of Stress Resistance.

EARLY-STAGE SYMPTOMS	MID-STAGE SYMPTOMS	LATE-STAGE SYMPTOMS
<p>High stress</p> <p>Appear high strung, anxious, or agitated</p> <p>occasional sleeplessness, but little fatigue ('tired, but wired')</p> <p>Higher pulse</p>	<p>Moderate stress</p> <p>Tired</p>	<p>Fatigued/exhausted</p> <p>Very tired in the evening</p> <p>Occasional sleeplessness (difficulty falling asleep and staying asleep)</p> <p>Low pulse</p>



Lifestyle and Nutritional Support

The ability to respond to stress has the potential to interfere with the enjoyment of life and even the ability to perform ordinary daily activities. Incorporating lifestyle, nutritional, and behavioral recommendations can help support healthy HPA axis function. Although specific recommendations differ based on the stage of stress resistance, below are a few considerations:

- Obtain regular exercise
- Establish regular bed times and obtain sufficient sleep
- Practice relaxation activities (e.g., meditation, yoga, hobbies)
- Consider smoking cessation programs
- Avoid or limit alcohol and sugar consumption
- Identify and remove food intolerances

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Supplemental Considerations for HPA Optimization

Integrative Therapeutics HPA Axis Optimization Program offers healthcare professionals quality nutritional supplements to support the health and well-being of patients in various stress response stages. It provides a comprehensive, yet flexible, approach to individualized patient care. To learn more about the HPA Axis Optimization Program, visit integrativepro.com/HPA.

Early-Stage

In the Early-Stage of stress resistance, patients can benefit from supplementation with herbs and nutrients that calm HPA axis activation, support healthy cortisol balance, and help relieve occasional anxiety and stress.*

- **Ashwagandha** (*Withania somnifera*) has been shown in clinical studies to reduce stress and occasional anxiety in adults.*^{9,10} A literature review demonstrated that ashwagandha exerts “positive influence on the endocrine, cardiopulmonary, and central nervous systems.”*¹¹
- **L-Theanine**, an amino acid found in green tea, has been shown to inhibit cortical neuron excitation, thereby creating feelings of calm, supporting blood pressure already within normal limits, and improving mood.*¹²
- **Magnolia** (*Magnolia officinalis*) has been shown to provide calming effects, which can be in part attributed to its interaction with receptors for the neurotransmitter gamma-aminobutyric acid (GABA).^{*13}
- **Phosphatidylserine** (PS) has been shown to support an adaptive cortisol response to stress.* One study involving young adults demonstrated that PS positively influenced feelings of stress, heart rate, and mood.*¹⁴

Mid-Stage

Patients in the Mid-Stage of the stress response can benefit from adaptogens, which are botanical ingredients that support the body’s ability to respond to stress and restore homeostasis.* This may, in turn, influence mood, cognition, and energy levels.*

- **Rhodiola** (*Rhodiola rosea*) is an adaptogen that that helps to reduce occasional fatigue, improve mood, and promote psychological adaptation.*¹⁵
- **Holy basil** (*Ocimum tenuiflorum*) prevents reductions in brain catecholamine and monoamine oxidase levels and may increase dopamine and serotonin levels during stress.*¹⁶
- **Eleuthero** (*Eleutherococcus senticosus*) supports adrenal function, regulates neurotransmitters, and may increase resistance to stress.*¹⁷
- **Ashwagandha** (*Withania somnifera*) may modulate hormonal changes that occur during stress.*
- **Maca** (*Lepidium meyenii*) has been shown in preliminary human research to have a positive influence on mood, feelings of occasional anxiety, and libido.*¹⁸⁻²⁰

Late-Stage

In the Late-Stage, patients can benefit from adrenal-supportive nutrients and botanicals to support healthy cortisol production.* Fortifying the diet with essential vitamins that can be depleted by stress is also important in maintaining adrenal cortex function, combatting occasional stress-related fatigue, and promoting energy recovery.*

- **Vitamin B1** (thiamine) is a water-soluble, sulfur-containing member of the B vitamins; the coenzyme form of thiamine plays a role in energy production.*²¹
- **Vitamin B2** (riboflavin) is necessary for energy production as well as normal cell function and growth.*²² Animal research shows that a riboflavin deficiency leads to an initial increase, followed by a decrease, in adrenal cortex activity.*²³
- **Vitamin B5** (pantothenic acid) is involved in numerous biological reactions, including the production of energy and the synthesis of steroid hormones, including cortisol.*²⁴ Vitamin B5 is required for normal function of the adrenal cortex.*²⁵
- **Vitamin B6** (pyridoxine) is a cofactor for approximately fifty different enzymes and plays a role in the production of neurotransmitters, such as serotonin, dopamine, epinephrine, norepinephrine, and gamma-aminobutyric acid (GABA).*^{26,27}
- **Forskolin**, the active constituent in *Coleus Forskohlii*, has been shown in several *in vitro* studies to support pituitary ACTH production and steroidogenic gene transcription in human adrenal cells.*^{28,29}
- **Licorice** (*Glycyrrhiza glabra*) root extracts have been shown to influence cortisol production in both animals and humans by inhibiting 11beta-hydroxysteroid dehydrogenase, the enzyme responsible for converting cortisol to cortisone.*³⁰⁻³² In one study, supplementing with licorice extract increased saliva cortisol levels in healthy women.*³³



Late-Stage Sleep Support

Sufficient quality sleep is vital to overall health and well-being. Sleep plays a modest but important role in modulating HPA axis activity by inhibiting cortisol secretion as part of the daily rhythm that controls sleep and wakefulness. Disruptions in this cycle due to abrupt shifts in sleep duration or sleep quality have been found to disturb the daily cortisol rhythm.³⁴ Conversely, activation of the HPA axis can lead to arousal and occasional sleeplessness.³⁵ Supporting sleep efficiency and the daily cycle of cortisol secretion may positively influence daytime performance and a normal stress response.^{*36}

- **Melatonin** is synthesized from tryptophan and secreted by the pineal gland during periods of darkness.³⁷ Human research has found that supplemental melatonin promotes sleep, improves sleep quality, and shortens sleep onset latency, particularly in people age 55 and older.^{*38-41}
- **Curcumin**, a key constituent of turmeric (*Curcumin longa*), possesses powerful antioxidant properties.⁴² Preliminary animal research suggests that curcumin may help fight oxidative stress and support normal behavior during periods of occasional sleeplessness.^{*43}
- **L-Theanine** has been shown to increase serotonin and dopamine levels in animals⁴⁴ and in humans,⁴⁵ which may promote muscle relaxation and improved sleep.*
- **Glycine** is an inhibitory neurotransmitter in the central nervous system. Clinical trials involving healthy human volunteers show that glycine positively influences sleep quality.^{*46-49}
- **5 HTP** (L-5-Hydroxytryptophan) is a serotonin precursor that supports sleep regulation.^{*50} In a small double-blind trial, supplementation with 5-HTP increased rapid-eye-movement (REM) sleep, which may suggest improved sleep quality.^{*51}



Early-Stage

Cortisol Manager™ stress hormone stabilizer

Helps reduce stress hormones and promote relaxation without the use of habit-forming ingredients.*

Cortisol Manager can be taken in conjunction with HPA Adapt when additional energy and stress support is needed.*



One tablet contains: Stress-Reducing Proprietary Blend: ashwagandha (*Withania somnifera*) (Sensoril® brand) root and leaf extract and L-theanine (Suntheanine® brand) 250 mg; Cortisol-Reducing Proprietary Blend: magnolia (*Magnolia officinalis*) bark extract standardized to contain 2% honokiol and 1% magnolol and epimedium (*Epimedium koreanum*) aerial part extract 225 mg; Phosphatidylserine 50 mg.

Other ingredients: Dextrose, cellulose, modified cellulose gum, modified cellulose, magnesium stearate, stearic acid, titanium dioxide color, vegetable glycerin, soy lecithin, and carnauba wax.

Contains no: Yeast, wheat, gluten, dairy products, artificial flavoring, preservatives, or ingredients of animal origin. All colors used are from natural sources.

Recommendations: Take 1 tablet before bedtime, or as recommended by your healthcare professional. Increase to 2 tablets during times of high stress. Safe for use every night.

Warning/caution: If pregnant, nursing, taking prescription drugs, or if you suffer with chronic insomnia, consult your healthcare professional prior to use. Keep out of reach of children.

Item #: 70453 **Form:** 30 Tablets
Item #: 70459 **Form:** 90 Tablets

Mid-Stage

HPA Adapt™ stress resistance complex

Combines five powerful adaptogenic herbs to maintain a healthy stress response and support stress hormone balance via the HPA axis.*



Four capsules contain: Rhodiola (*Rhodiola rosea*) Root Extract standardized to contain 3% rosavins and 1% salidroside 400 mg; Ashwagandha (*Withania somnifera*) (Sensoril® brand) Root and Leaf Extract 300 mg; Eleuthero (*Eleutherococcus senticosus*) Root Extract 300 mg; Holy Basil (*Ocimum sanctum*) Leaf Extract standardized to contain 2.5% triterpenoic acids including ursolic and oleanolic acids 200 mg; MacaPure™ brand Maca (*Lepidium meyenii*) Root Extract standardized to contain 0.6% macaenes and macamides 150 mg.

Other ingredients: Vegetable capsule (modified cellulose), ascorbyl palmitate and silicon dioxide.

Contains no: Sugar, salt, yeast, wheat, gluten, soy, dairy products, artificial coloring, artificial flavoring, preservatives, or ingredients of animal origin.

Recommendations: Take 2 to 4 capsules daily on an empty stomach or as recommended by your healthcare professional.

Warning/caution: Do not use if pregnant. If nursing or taking prescription drugs, consult your healthcare professional prior to use.

Item #: 10270 **Form:** 120 Veg. Capsules

Additional Early and Mid-Stage Considerations:

Lavela WS 1265™	Item #: 70662	Form: 60 Softgels
L-Theanine	Item #: 79556	Form: 60 Veg. Capsules
Phosphatidylserine, soy-free	Item #: 70657	Form: 60 Softgels

Sensoril® is protected under US Patent 6,713,092 and is a trademark of Natreon, Inc.
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Late-Stage

CortiVive™ adrenal response formula

Helps support adrenal function for healthy cortisol production and helps combat stress-related fatigue to promote energy recovery.*



Two capsules contain: Vitamin C (ascorbic acid) 30 mg; Thiamin (as thiamin HCl) (vitamin B1) 3 mg; Riboflavin (as riboflavin-5'-phosphate and riboflavin) 3.4 mg; Vitamin B6 (as pyridoxal-5'-phosphate and pyridoxine HCl) 6 mg; Pantothenic Acid (as calcium D-pantothenate) 150 mg; Proprietary Blend: Eleuthero (*Eleutherococcus senticosus*) Root Extract standardized to contain 0.8% eleutherosides, Licorice (*Glycyrrhiza glabra*) Root and Rhizome Extract and *Coleus forskohlii* Root Extract standardized to contain 20% forskolin (10 mg) 350 mg.

Other ingredients: Vegetable capsule (modified cellulose), cellulose, ascorbyl palmitate, and silicon dioxide.

Contains no: Sugar, salt, yeast, wheat, gluten, soy, dairy products, artificial coloring, artificial flavoring, preservatives, or ingredients of animal origin.

Recommendations: Take 2 capsules one to two times daily, or as recommended by your healthcare professional.

Warning/caution: If pregnant, nursing, or taking prescription drugs, consult your healthcare professional prior to use.

Item #: 10303 **Form:** 120 Veg. Capsules

Sleep Reset™ restful sleep blend

Supports the ability to fall asleep and stay asleep, enhancing overall sleep quality without morning drowsiness.*



One sachet contains: Vitamin B6 (as pyridoxine HCl) 50 mg; Glycine 3 g; Proprietary Blend: Theracurmin® (water-dispersible turmeric (*Curcuma longa*) rhizome), L-Theanine and L-5-Hydroxytryptophan (5-HTP) 300 mg; Melatonin 3 mg.

Other ingredients: Natural flavors, orange fruit powder, citric acid, silicon dioxide, xanthan gum, and vegetable color.

Contains no: Sugar, salt, yeast, wheat, gluten, soy, dairy products, artificial flavoring, preservatives, or ingredients of animal origin. All colors used are from natural sources.

Recommendations: Mix the contents of 1 sachet with water 30 minutes before bedtime or as recommended by your healthcare professional.

Warning/caution: If pregnant, nursing, or taking prescription drugs, consult your healthcare professional prior to use.

Item #: 10285 **Form:** 30 Sachets

Additional Late-Stage Considerations:

Adrenal Cortex-Fractions	Item #: 74085	Form: 60 Capsules
DHEA-5	Item #: 75006	Form: 60 Veg. Capsules
DHEA-25	Item #: 75026	Form: 60 Veg. Capsules

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