HPA AXIS & ADRENAL DYSFUNCTION
AN EVIDENCE BASED DISCUSSION OF TREATMENT MODALITIES

Lena D. Edwards, MD, FAARM
Internal Medicine
Anti-Aging and Regenerative Medicine

OBJECTIVES OF DISCUSSION
- Discuss the importance of lifestyle modification and institution of stress reduction techniques as an essential component of treatment
- Discuss the effects of sleep disturbances on adrenal dysfunction and review viable treatment options
- Review the vitamins, minerals, and other supplements beneficial in the treatment of adrenal dysfunction
- Discuss the evidence for and clinical utility of adrenal and multiglandular extracts
- Define the term plant adaptogen and discuss some of the most well studied adaptogens used in treating adrenal dysfunction
- Discuss the appropriate use of pharmacologic agents in the treatment of adrenal dysfunction
- Review clinically relevant case studies

DEFINITION OF ADRENAL DYSFUNCTION
The inability of the adrenal glands to produce adequate amounts of stress hormones in a normal diurnal pattern, whether primarily or secondarily, in response to allostatic load ultimately resulting in HYPOCORTISOLISM

PROPOSED PROGRESSION TO ADRENAL DYSFUNCTION

SUMMARY OF TREATMENT MODALITIES
- Stress reduction techniques
- Sleep hygiene
- Lifestyle modification
- Vitamins and minerals
- Glandular extracts
- Plant adaptogens
- Pharmacologic therapy

STRESS REDUCTION TECHNIQUES
- Identify and eliminate stressors
- Adjust attitude or response to the stressor
- Eat regular meals; adequate mastication
- Gentle exercise
  - Tai Chi
  - Yoga
  - Pilates
**STRESS REDUCTION TECHNIQUES**

- Spirituality/Religiousity
- Dietary modification
- Meditation
- Adequate sleep
- Rest & Relaxation
  - Frequent daily breaks

**MEDITATION**

- Reduces stress induced cortisol secretion
- Increases levels of brain derived neurotrophic factor thereby conferring neuroprotection
- Reduces levels of Interleukin-6
- Improved cortisol release patterns and immune function → improved quality of life and stress tolerance in breast and prostate cancer survivors

*Psychoneuroendocrinology. 34(1):87-98, 2009 Jan.*

**DIETARY MODIFICATION**

- Ingest good quality protein
- Combine unrefined carbohydrates (whole grains) with good quality protein and oils (nuts and seeds) at most meals.
- Use cold pressed oils - olive, walnut, filbert, flax
- Emphasize vegetables (alkaline foods)
- Small frequent meals throughout the day

*Seminars in Gastrointestinal Disease. 10(1):14-9, 1999 Jan.*
*Physiology & Behavior. 64(3):311-5, 1998 Jun 1.*

**DIETARY MODIFICATION**

- Avoid the following
  - Hydrogenated fats
  - Caffeine
  - Chocolate
  - Refined carbohydrates
  - Junk foods
  - Allergenic or sensitive foods
- Digestive aids may be needed by most until recovery is more complete
- Allow *unrefined* salt to be added

**SLEEP HYGIENE**

**TREATMENT OF ADRENAL DYSFUNCTION**
**Consequences of Sleep Deprivation**

- Activation of the sympathetic nervous system
- Dysregulation and activation of the HPA axis
- Nocturnal CRH hyperreactivity
- Sleep fragmentation or nocturnal awakenings cause increased nocturnal pulsatile release of cortisol
- Subsequent HPA axis dysregulation induces hypercortisolism which further fragments sleep

**Insomnia**

- Behavioral modification
- Sleep hygiene
  - Regular sleep-wake cycle
  - Stress reduction techniques
- Avoid prescription sleep aids and alcohol
- Bedroom is to be used for sleep and intimacy only
- Avoid third shift work

**Sleep Disturbances**

- 5-HTP (25 to 300 mg QHS)
- Melatonin (0.5 to 6 mg (SR better) 30 to 60 minutes before bedtime)
- Seditol (365 to 730 mg QHS)
- Phosphatidylserine (300 mg 60 to 90 minutes before bedtime)
- L-Theanine (100 to 200 mg 30 to 60 minutes before bedtime)
- Calming herbs (Valerian root, Chamomile, Hops, Passion flower)
- Magnesium Glycinate (400 to 800 mg QHS)

**Pharmacologic Treatments**

- Glucocorticoid Receptor Antagonists (Mifepristone)
  - Suppress amygdala driven CRH activation
  - Resets HPA axis upon discontinuation
- Mineralocorticoid agonists (Fludrocortisone)
  - Augments nocturnal hippocampal suppression of CRH
- CRH-R1 antagonist (Antalarmin)
  - Antagonizes effects of CRH
OBSTRUCTIVE SLEEP APNEA

Affects 1 in every 22 people in this country... approximately 12 million and rising

OBSTRUCTIVE SLEEP APNEA

Intermittent hypoxia
Recurrent cerebral arousals
HPA axis activation

OBSTRUCTIVE SLEEP APNEA

Nocturnal Hypercortisolism

Impaired cortisol release pattern
Lack of cortisol suppression to ACTH

Therapy with CPAP
- Improvement in nocturnal salivary hypercortisolism
- Reduction in SNS induced tachycardia
- Improved cortisol suppression after low dose dexamethasone
- Decreases nadir cortisol concentrations
- Reversed dampening of normal nocturnal HPA axis oscillation

Metab Clin & Experimental. 58: 848-853, 2009

TREATMENT OF ADRENAL DYSFUNCTION

VITAMINS AND MINERALS

- Magnesium (400 mg daily, Glycinate or Citrate form)
- Vitamin C (2 to 5 grams daily)
- B Vitamins (especially B5 up to 1.5 grams daily)
- Selenium
- Zinc
- Calcium (800 to 1000 mg daily)
- Copper
- Sodium
- Manganese
- Vitamin E with mixed tocopherols (800 IU daily)
MAGNESIUM

- Primary functions of magnesium:
  + Calcium antagonist
  + Membrane function
  + Energy transfer

  Critical component of over 300 enzymatic pathways

- Intense physical stress increases magnesium loss via bodily fluids
- Intense physical activity, cell membranes' permeability increases increasing magnesium requirement
- Serum inadequate measure of total body magnesium since 99.7% of total body magnesium is located in the bones and cells
- Increased supplies of magnesium increase insulin sensitivity to glucose
- Magnesium homeostasis exerts an anti-stress effect

Cardiovascular Drugs and Therapy. 12: 197-202, 1998

VITAMIN C (ASCORBATE)

- Both the adrenal medulla and the adrenal cortex accumulate high levels of ascorbate
- ACTH stimulation results in adrenal release of ascorbate
- During periods of stress, adrenal glands release vitamin C which has been found to have primarily a local, rather than systemic, effect to:
  + Increase nitric oxide production or synthesis to promote cortisol release
  + Modifies ACTH receptor sensitivity
  + Local vasodilation to increase cortisol delivery

Endocrine Research. 30(4): 871-875, 2004
**VITAMIN C (ASCORBATE)**

- 2001 study in ultramarathon runners

  “Supplementation with vitamin C may blunt the adaptive mobilization of this vitamin from the adrenals during exercise-induces oxidative stress and may be associated with an enhancement of the acute phase protein response and attenuation of the exercise-induced increase in serum cortisol.”


**OTHER NUTRIENTS**

- Curcumin
  - Inhibits ACTH stimulation of cortisol release
  - Inhibits Angiotensin II stimulation of cortisol release
- Thiamine
  - Prevents post-surgical hypercortisolemia
- Pantothenol
  - Increases urinary excretion of 17-hydroxyketo steroids
  - Increase glucocorticoid production

  (Journal of Natural Products. 72(8):1533-7, 2009
  Bollettino Societa Italiana Biologia Sperimentale. 57(18): 1869-72, 1981)

**GLANDULAR EXTRACTS**

- Invented and made commercially available in 1931.
- Heavily researched in the 1940’s as potentially effective for altitude induced adrenal stress in military pilots
- Use does not decrease endogenous hormone production
- May assist in adrenal gland self repair

**ADRENAL GLANDULAR EXTRACTS**

- Contain small amounts of cortisone and other adrenal hormones
- Preparations may also contain peptides which promote endogenous adrenal hormone production
- Multi-glandular extracts
  - Contain adrenal, hypothalamus, pituitary, thyroid, and/or gonadal extracts
  - Do not use as monotherapy or as alternative to standard medical treatment

**STUDIES ON CLINICAL EFFICACY OF GLANDULAR EXTRACTS**

- Porcine thyroid glandular extracts may potentiate ACTH induced corticosterone production (Endocrinologia Japonica. 31(4):443-9, 1984 Aug.)
- Administration of adrenal cortical extracts in a 1950 study showed (Blood. 5(8):732-41, 1950 Aug.):
  - Reduced eosinophils and lymphocytes in normal patients
  - Reduction in lymphocytosis in patients with infectious mononucleosis
STUDIES ON CLINICAL EFFICACY OF GLANDULAR EXTRACTS

- MANY clinical studies were conducted in the 1950’s in Russia, Germany, and Italy
- Some clinical utility of adrenal cortex preparations:
  - Surgery
  - Tuberculosis
  - Psoriasis
  - Diabetes
  - Various inflammatory diseases in children

Keep in Mind.....

Glandular extracts may not be helpful in patients whose hypocortisolism is not adrenally mediated

TREATMENT OF ADRENAL DYSFUNCTION

PLANT ADAPTOGENS

**ADAPTOGENS: DEFINITION**

“Compounds that increase the ability of an organism to adapt to environmental factors and to avoid damage from such factors”


**ADAPTOGENS: OVERVIEW**

- Promote physiological resistance of organism to stress, fatigue, trauma, and anxiety
- Used for thousands of years in ancient Chinese & Indian medicine
- Research on adaptogens began in the 1940’s


**ADAPTOGENS: ALL ABOUT BALANCE**

- **Adrenaline**
  - Switch on hormone
- **Cortisol**
  - • Switch off hormone
  - • Protects against over-reaction
- **Nitric Oxide**
  - • Hormone biosynthesis
  - • Modulates and organ hormone effects


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**ADAPTOGENS: MECHANISM OF ACTION**

- Stress agonist effects on HPA axis regulation
- Stimulate the nervous system in a different manner than traditional stimulants
  + Regulation of elements of the stress system
  + Modulate stimulus-response coupling
- Control key mediators of stress
  + Hsp70*
  + JNK1(c-Jun-N-terminal protein kinase)
  + Forkhead Box O transcription factor DAF-16
  + Cortisol
  + Nitric oxide


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**ADAPTOGENS: MECHANISM OF ACTION**

**Key Point of Action**

Adaptogens cause up regulation and stress mimetic effects on the stress sensor protein

**Hsp70**


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**ADAPTOGENS: MODES OF ADMINISTRATION**

- Single dose application
  + Important in situations that require a rapid response to strain
  + Effects are associated with the sympatho-adrenomedullary system
  + Increases levels of
    - Catecholamines
    - Neuropeptides
    - ATP
    - Nitric oxide
    - Eicosanoids


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**ADAPTOGENS: TYPES OF ADMINISTRATION**

- Repeated dose application
  + Stress positive effect in a manner similar to physical exercise leading to increased endurance and stamina
  + Does not inhibit the stress response but rather acts as a stress agonist to induce adaptive responses to stress
  + Particularly useful in sports medicine by increasing physical endurance and promoting enhanced recovery

ADAPTOGENS: SUBCLASSES

- Triterpenes
  - Saponins
  - Dammarane
  - Curcurbitacins
  - Phytosterols
  - Beta-sitosterol
  - Phytoecdysteroid
  - 20-ecdysone
  - Turkesterone

- Phenylpropanes
  - Flavinoids
  - Glucopyranoside
  - Prenylated flavonoids
  - Flavan glycosides
  - Lignans
  - Schizandrin
  - Sesamin
  - Syringaresinol

- Oxylipins
  - Hydroxylated fatty acids
  - Licorice
  - Glycyrrhiza

ADRENAL ADAPTOGENS

- Ashwaganda
- Rhodiola
- Panax Ginseng
- Licorice
- Cordyceps
- Relora
- Maca
- Holy Basil
- Bacopa
- Schisandra
- Astragalus
- Siberian Ginseng

ADAPTOGENS: ASHWAGANDA

- *Withania somnifera*
- Cardioprotective
- Augmentation of endogenous anti-oxidant production
- Reduces tumor cell proliferation
- Dose related anti-stress activity
- Stimulate thyroid function
- Free radical scavenger
- Neuroprotective

- Immunomodulatory
- Rejuvenating
- Used as an adjunct in several CNS disorders (Parkinson’s, cerebral ischemia, Alzheimer’s disease, tardive dyskinesia)
- Adjunctive utility in drug addiction
- Completely safe...no adverse side effects reported
- Typical dose is 3 to 6 grams daily
**ADAPTOGENS: HOLY BASIL**

- Ocimum Sanctum
- Also known as Indian Ginseng
- Stimulates insulin secretion
- Protects pancreatic beta cells
- Antioxidant
- Reduces lipid peroxidation
- Free radical scavenger
- Cardioprotective during chronic stress

**ADAPTOGENS: HOLY BASIL**

- Improves physical endurance
- Modulates adrenal corticosterone levels
- Lowers cholesterol
- Immunomodulator
- Anti-bacterial activity against Neisseria gonorrhea
- Possible antidepressant activity
- Typical dose 400 – 800 mg BID (std. to 1% ursolic acid)

**ADAPTOGENS: RHODIOLA**

- Rhodiola rosea
- Also known as Golden/Arctic Root
- Native to the Himalayas, Parts of Europe, Arctic
- Regulates brain function
- Improves mental performance
- Improves ability to concentrate
- May help patients with stress induced mental and physical fatigue

**ADAPTOGENS: RHODIOLA**

- Improves physical endurance
- Radioprotective
- Anti-cancer
- Anti-oxidant
- Superoxide ion radical scavenger
- Improves attention, cognition, and mental performance in fatigue and chronic fatigue syndrome

**ADAPTOGENS: RHODIOLA**

- Improves visual acuity
- Prevents stress induced adrenal catecholamine depletion
- Reduces levels of circulating C-reactive protein
- Influences levels and activity of monoamines and opioid peptides
- 250 mg QD to TID (3-5% rosavin + 1-3% salidroside)

**ADAPTOGENS: SCHIZANDRA**

- Generates alterations in the basal levels of nitric oxide and cortisol in blood and saliva with subsequent effects on the blood cells, vessels and CNS
- Increases physical work capacity and endurance
- Improves mental function, mental capacity, and mental accuracy
- Reduces fatigue, muscle pain, shortness of breath after extreme physical activity

Olsson et al. Planta Med. 2009; 75: 105-112


**ADAPTOGENS: SCHIZANDRA**

Numerous clinical trials have demonstrated the efficacy of Schizandra in:

- Mood disorders
- Asthenia
- Neuralgic disorders
- Alcoholism
- Psychiatric disorders
  - Neurosis
  - Psychogenic depression
  - Astheno-depressive states
  - Schizophrenia


**ADAPTOGENS: SCHIZANDRA**

- Hypotension and cardiotonic disorders
- Infectious diseases
  - Influenza
  - Chronic sinusitis
  - Otitis
  - Neuritis
  - Otosclerosis
  - Pneumonia

**ADAPTOGENS: MACA**

- Lepidium peruvianum
  - Employed by the Incas and other cultures in the Andean region for its aphrodisiac and fertility enhancing powers
  - Improves sperm production and motility independent of hormones
  - Eliminates variations in homeostasis induced by stress


**ADAPTOGENS: MACA**

- Reduces stress induced adrenal hyperplasia
- Eliminates stress induced ulcers
- Reduces corticosterone levels
- Reduces stress induced hyperglycemia
- Dose: 5-10 grams BID dried powder

**ADAPTOGENS: LICORICE ROOT**

- Glycyrrhiza glabra
  - Inhibits 11 beta hydroxysteroid Dehydrogenase thereby blocking cortisol’s transformation into cortisone
  - Higher doses reduce testosterone levels in PCOS
  - Improves memory (decreases Ach’ase)
  - Antibacterial
  - Inhibits tumor cell angiogenesis
  - Antidepressant
  - Adrenocorticoid-like activity
**ADAPTOGENS: LICORICE ROOT**
- Protects mitochondrial function during periods of oxidative stress
- lowers cholesterol
- Anti-fungal and anti-viral
- Anti-ulcer
- Decreases abdominal adiposity
- Reduces adrenal stress
- Dose 2 – 3 grams daily (200-300 mg of Glycyrrhiza); ½ tsp solid extract 8am and ¼ tsp at noon

**ADAPTOGENS: GINSENG**
- Normalizes cortisol levels
- Immunostimulant
- Anti-fatigue
- Prevents oxidative stress
- Improves cognitive performance
- Anti-depressant
- Suppresses inflammation and DNA damage

**ADAPTOGENS: GINSENG**
- Korean ginseng most potent followed by American ginseng and Siberian ginseng
- Use caution in hypertensive patients
- Use caution in patients on medications for diabetes, cardiac glycosides, and stimulants
- For chronic fatigue, 2-4 grams TID
- Typical dose 2-8 grams of dried root daily

**TREATMENT OF ADRENAL DYSFUNCTION**

**HERBAL SUPPLEMENTS**

**THEANINE**
- Amino acid extracted from green tea leaves
- Increases alpha brain wave activity
- Inhibits LDL oxidation
- Counteracts stimulatory effects of caffeine
- Reduces blood pressure

**THEANINE**

- Influences the secretion and function:
  - Dopamine
  - Serotonin
- Exerts anti-stress effects during an acute stress challenge
- Dose dependent presence of brain alpha waves within 40 minutes of ingesting 200 mg 


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**PHOSPHATIDYLSERINE**

- Ubiquitous phospholipid
- Only phospholipid in animal cells containing an amino acid
- Found on the inner leaflet of cell membranes
- Important in cellular communication and excitability
- Induces release of acetylcholine, dopamine, and norepinephrine
- Dampens stress induced ACTH and cortisol release


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**CORTISOL VS. HYDROCORTISONE**

- Physiologic doses (15 mg) do not increase levels beyond normal levels
- Physiologic doses do not cause bone loss, adrenal suppression, or immune suppression
- Typical dosing schedule:
  - 10 to 15 mg in am
  - 5 to 10 mg at noon
  - 2.5 to 5 mg late afternoon

Holtorf KH. J Chronic Fatigue Syn. 2008; 14(3):1-14

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Holtorf KH. J Chronic Fatigue Syn. 2008; 14(3):1-14
HYDROCORTISONE

- Improves cellular and humoral immunity
- Therapeutic trial of low dose hydrocortisone should be considered in patients with signs and symptoms of adrenal dysfunction, even if test results 'normal'.
- Has been shown to be effective treatment in patients with CFS and fibromyalgia

Holtorf KH. J Chronic Fatigue Syn. 2008; 14(3):1-14
Cleare AJ. The Lancet. 1999; 353: 455-458

HYDROCORTISONE

Holtorf and colleagues conducted multi-center trial of 4000 consecutive patients. Conclusion...

“Supplementation has been shown to be a beneficial and safe alternative with little of no risk as part of a multi-system integrative treatment protocol in patients with fibromyalgia and chronic fatigue syndrome [related to adrenal dysfunction].”

Holtorf KH. J Chronic Fatigue Syn. 2008; 14(3):1-14

FLUDROCORTISONE

- Mineralocorticoid and glucocorticoid activity
- Can be used to temporarily treat orthostatic hypotension
- Potential side effects: hypertension, edema, headaches

DHEA

- Use caution in patients with low cortisol since it can further lower cortisol levels. Counter-regulatory hormone to cortisol
- Typical dose in women 2.5 to 10 mg daily and 25 to 50 mg daily in men
- Use 7-keto form in patients who are not testosterone and/or estrogen deficient

DHEA

- Has been shown to prevent diabetes, hepatitis, and colon cancer (J Steroid Biochem Mol Biol, Jun 1, 2003; 85(2-5): 469-472)
- Replacement may also be helpful in auto-immune diseases, insulin resistance, osteoporosis, and atherosclerosis (Evid Based Compl Alter Med. 2005; 2(3): 413-419)
**CLINICAL CASES: CASE I**

- **66 year old postmenopausal female**
- **Symptoms**
  - Exhaustion
  - Difficulty losing weight
  - Dyspepsia
  - Polyarthralgia
  - Impaired memory
  - BLE edema
  - “Pain all over”
  - Depression
  - Insomnia

**IMPORTANT ASPECTS OF TREATMENT**

- Genetic predisposition
- Past medical history
- Medications & Supplements
- Clinical symptoms

**CLINICAL CASES: CASE I**

- **Past Medical History**
  - Type 2 DM
  - Asthma
  - Hypertension
  - Hyperlipidemia
  - Fibromyalgia
  - Hypothyroidism
  - Restless leg syndrome
  - Esophageal dysmotility
  - Depression
  - Chronic insomnia

- **Medications**
  - Advair
  - Singularair
  - Mirapex
  - Ambien
  - Zocor
  - Cymbalta
  - Lexapro
  - Flexeril
  - Kadipex

**CLINICAL CASES: CASE II**

- **41 year old pre-menopausal female**
- **Clinical symptoms**
  - Fatigue
  - Difficulty losing weight
  - Diffuse joint pain
  - Depression
  - Anxiety
  - Irregular menstrual cycles

**CLINICAL CASES: CASE II**

- **Past medical history**
  - Seasonal allergies
- **On no prescription medications or supplements**
**CLINICAL CASES: CASE II**

- 51 year old obese male

**Clinical symptoms**
- Daytime fatigue
- Depressed mood
- Impaired concentration
- Decreased stamina
- Diminished libido
- Insomnia (initiation and propagation)

**CLINICAL CASES: CASE III**

- 51 year old obese male

**Clinical symptoms**
- Daytime fatigue
- Depressed mood
- Impaired concentration
- Decreased stamina
- Diminished libido
- Insomnia (initiation and propagation)

**Past medical history**
- Insulin resistance
- Dyslipidemia
- Hypertension
- Depression
- Erectile dysfunction

**Medications**
- Venlafaxine
- Metformin
- Aspirin
- Lipitor
- Lunesta

**CLINICAL CASES: CASE IV**

- 30 year old female

**Past medical history**
- Unremarkable

**Medications**
- YAZ
- Claritin

**Clinical symptoms**
- Fatigue
- Depression
- Insomnia
- Weight gain
- Impaired memory
CLINICAL CASES: CASE IV

- 62 y.o. postmenopausal female
- Symptoms:
  - Fatigue
  - Difficulty losing weight
  - Polyarthralgia
  - Depression
  - Anxiety
  - Insomnia
  - Sugar cravings
  - Dyspepsia

CLINICAL CASES: CASE V

- Past medical history
  - Degenerative joint disease
  - Depression
  - GERD/Hiatel hernia
  - TAH + BSO
  - R. hip replacement
  - Obesity
  - Metabolic syndrome

- Medications
  - Mobic
  - Citalopram
  - Omeprazole
  - Premarin
  - Ambien