The Stress Response, Women’s Health & the Role of Adaptogens

Aviva Romm, MD
July 27, 2016
Michael Chapman, ND
Medical Education Specialist - Asheville
Technical Issues & Clinical Questions

• Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

• We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.

DISCLAIMER: Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.
Need More Resources?

Ensure you have an account!
The Stress Response, Women’s Health & the Role of Adaptogens

Aviva Romm, MD
July 27, 2016
Disclaimer

- The suggested dosages are for educational purposes only.
- They are suggestions for patients with normal renal and hepatic function.
- They are not intended as a substitute for a personalized approach to each patient but are designed instead to be a guideline.
- Genova Diagnostics and Aviva Romm, MD, are not responsible for any adverse effects or consequences resulting from the use of any of these suggestions or preparations in this seminar.
Women & Stress

- 75% - 90% of doctor visits are for stress-related ailments/concerns
- APA 75% of all Americans have moderate to severe stress
- 30% more likely to report experiencing a great deal of stress
- Greater physical and emotional symptoms of stress than men:
  - Headache (41% vs. 30%),
  - Weepiness (44% vs. 15%),
  - Stomach upset or indigestion (32% vs. 21)
- Lean in, do it, have it all, be it all
Allostatic Load

“The price the body pays over long periods of time for adapting to challenges.”
Measuring for Allostatic Load: 
*MacArthur Study of Successful Aging*

**Primary Mediators**
- Cortisol (overnight)
- Catecholamines
- DHEA-S

**Secondary Mediators**
- Waist-to-Hip
- S:D BP Ratio
- Albumin
- Total Cholesterol and HDL
- Hemoglobin
- Fibrinogen
- CRP
Beyond Salt, Sugar, Fat: Cravings, Obesity, and Insulin Resistance

• Allostatic load is a major driver of fat, sugar, and salt consumption
• Fuel for HPA axis responses
• Major determinant of insulin resistance
• Chronically high levels of Glucocorticoids (GC’s) →
  – Increase CRF mRNA in amygdala – a critical node in the emotional brain
  – GC’s increase the salience of pleasurable or compulsive activities (fat, sugar consumption) → ingestion of “comfort foods”
  – Self soothing: sugar, high fat foods QUIET the stress response via GC’s
  – Increased abdominal fat depots → decreased CRF release and GC’s into the brainstem.
  – Peripheral hormones that raise BP (angiotensin, aldosterone, and cortisol) modulate brain regions that stimulate hunger for sodium and energy-rich substrates
  – Chronically elevated appetite in the context of "industrial agriculture” is a recipe for "metabolic syndrome”
  – Relationship to eating disorders/ disordered eating (including orthorexia)
Women, Food, and Allostatic Load

- Women eat as a way to manage stress (31% women/21% men)
- Women report having eaten too much or eaten unhealthy foods because of stress in the past month far more often (49% women/30% men)
- 34% cite lack of willpower as a barrier to best health choices
- 56% say that for their willpower to improve, they’d have to feel less fatigue/more energy

Stress affects functioning of neurons in frontal cortex → Difficulty and poor decision making
Impact on Gut Health

- Emotion-gut connection
- Decreased intestinal blood flow
- Changes in intestinal milieu/balance of microflora → dysbiosis (Decreased *Lactobacillus* and *Bifidobacter*; increased *E. coli* and *Enterobacter*)
- Statistically significant shifts in the proportions of some species noted in individuals under conditions of anger or fear stress
- Decreased secretory IgA
- Decreased willpower and cravings → poor food choices → dysbiosis
Gut Health

Therapeutic interventions around gut microflora abundance and imbalance have proven helpful for clinical conditions.

Targeted therapy with dietary manipulation, prebiotics, and probiotics, to heal the gut may modulate commensal bacteria levels.
Cardiovascular Disease

Multiple pathways $\rightarrow$ to increased risk of CVD

- Increased reactivity of the fibrinogen system, CRP, IL-6, TNF, and platelets
- Activation of HPA-axis $\rightarrow$ hypercortisolemia $\rightarrow$ central obesity and insulin resistance
- Repeated sympathetic stimulation increases HR and BP $\rightarrow$ decreased HR variability, baroreflex dysfunction, and decreased myocardial electrical stability
- Decreased HR variability and higher morning cortisol
- Mental stress-induced ischemia with a decrease in LVEF associated with increased CV events over 5 years
INTERHEART: Loneliness & CVD

Loneliness, depression and hopelessness increased risk of CVD
> DM2, HTN, smoking, or obesity

• 11,119 cases and 13,638 controls
• Odds ratio (adjusted)
• Moderate or severe stress 1.65 for acute MI
• Permanent general stress 2.17 for acute MI
## Reproductive Function

<table>
<thead>
<tr>
<th>Hypothalamic–pituitary–adrenal axis</th>
<th>Effect on the female reproductive system</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRH</td>
<td>Inhibition of GnRH secretion</td>
</tr>
<tr>
<td>β-Endorphin</td>
<td>Inhibition of GnRH secretion</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Inhibition of GnRH and LH secretion, inhibition of ovarian estrogen and progesterone biosynthesis, inhibition of estrogen actions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reproductive CRH</th>
<th>Potential physiologic roles</th>
<th>Potential pathogenic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian CRH</td>
<td>Follicular maturation</td>
<td>Premature ovarian failure (↑ secretion)</td>
</tr>
<tr>
<td></td>
<td>Ovulation</td>
<td>Anovulation (↓ secretion)</td>
</tr>
<tr>
<td></td>
<td>Luteolysis</td>
<td>Corpus luteum dysfunction (↓ secretion)</td>
</tr>
<tr>
<td></td>
<td>Suppression of female sex steroid production</td>
<td>Ovarian dysfunction (↓ secretion)</td>
</tr>
<tr>
<td>Uterine CRH</td>
<td>Decidualization</td>
<td>Infertility (↓ secretion)</td>
</tr>
<tr>
<td></td>
<td>Blastocyst implantation</td>
<td>Recurrent spontaneous abortion (↓ secretion)</td>
</tr>
<tr>
<td></td>
<td>Early maternal tolerance</td>
<td></td>
</tr>
<tr>
<td>Placental CRH</td>
<td>Labor</td>
<td>Premature labor (↑ secretion)</td>
</tr>
<tr>
<td></td>
<td>Maternal hypercortisolism</td>
<td>Delayed labor (↓ secretion)</td>
</tr>
<tr>
<td></td>
<td>Fetoplacental circulation</td>
<td>Preeclampsia and eclampsia (↑ secretion)</td>
</tr>
<tr>
<td></td>
<td>Fetal adrenal steroidogenesis</td>
<td></td>
</tr>
</tbody>
</table>
“Chronic stress creates a hyper-reactive, hysterical amygdala, and this tells us tons about what stress has to do with anxiety disorders.” ~ R. Sapolsky

- Major depression affects women twice as often as men (15% vs 8%)
- 1 in 6 women on an antidepressant
- GAD twice as high in women as in men
- Exacerbations are worse during stressful times
- Women 2.5x more likely than men to use ADs; many on anxiety meds (Benzo anybody?)
- Chronic stress depletes dopamine; stress precipitates major depression
- Melancholic depression (MDD) associated with hyperarousal & HPA activation
- Atypical depression (MDD) associated with lethargy, fatigue, down-regulated HPA activation
Sleep Disturbance

• 49% of all women say they have lain awake at night in the past month because of stress
• Major presenting co-morbidity and QOL issue for women
• High PM, low AM cortisol, low DHEA common findings on adrenal stress testing via salivary tests
• Sleep affects everything – weight, food choices, self-regulation, mood, hormones, immunity (including cancer cell monitoring), cognitive function
Adrenocortex Stress Profile (Saliva)

• A salivary hormone test measuring 4 separate salivary samples over 24 hour period
• Provides insight into cortisol levels throughout the day as well as one early morning DHEA measurement
Adrenocortex Stress Profile (Saliva)

**Salivary Cortisol and DHEA**

Cortisol

- **Reference Range**
  - 1 Hour After Rising: 0.27-1.18 mcg/dL
  - 11AM - 1PM: 0.10-0.41 mcg/dL
  - 3PM - 5PM: 0.05-0.27 mcg/dL
  - 10PM - 12AM: 0.03-0.14 mcg/dL

**Hormone**

- DHEA 7am - 9am: 71-640 pg/mL
- DHEA: Cortisol Ratio x 10,000: 115-1,188

*Image: Genova Diagnostics*
One Day Hormone Check (Saliva)

**Salivary Cortisol and DHEA**

- **Cortisol**
  - Reference Range
  - 1 Hour After Rising
    - 7AM - 9AM: 0.27-1.18 mcg/dL
    - 11AM - 1PM: 0.10-0.41 mcg/dL
    - 3PM - 5PM: 0.05-0.27 mcg/dL
    - 10PM - 12AM: 0.03-0.14 mcg/dL

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA 7am - 9am</td>
<td>71-640 pg/mL</td>
</tr>
<tr>
<td>DHEA: Cortisol Ratio/10,000</td>
<td>115-1,188</td>
</tr>
</tbody>
</table>
Adrenocortex Stress Profile (Saliva)
Memory & Cognitive Function

- Acute stress $\rightarrow$ increases cortisol secretion $\rightarrow$ suppressed mechanisms in the hippocampus & temporal lobe that serve short-term memory
- Repeated stress $\rightarrow$ GCs and excitatory AA’s that $\rightarrow$ atrophy of dendrites of pyramidal neurons in the hippocampus
- Participates in emotional, verbal and “contextual” memory
- The hippocampus also regulates the stress response and acts to inhibit the response of the HPA axis to stress
- Sweden, population-based sample of 800 women, aged 38 to 54 years
- Chronically “stressed out,” jealous, moody, anxious or worried
- 38-year follow-up: 153 women developed dementia; AD was diagnosed in 104 cases
Immunity

• Repeated/chronic exposure to high allostatic load $\rightarrow$ different immunologic response than acute exposure
• Goes from beneficial to potentially pathological
• Repeated high allostatic load $\rightarrow$ recurrent endotoxemia, decreases reactivity of the HPA axis and decreases cytokine production
• Chronic allostatic load $\rightarrow$ suppressed cellular immunity
Immunity

Clinically:

• Increased susceptibility to and severity of common cold, increased cold-virus antibody titers
• Decreased healing time
• Chronic inflammation
• Autoimmunity > in women at critical times in lifespan due to decreased estrogens
• Higher levels of chronic stress have been associated with a higher rate of breast cancer, correlated with lower nfKB
"Inflamm-Aging"

Stress = Antigen; Antigen $\rightarrow$ conserved immunologic stress response

Upregulation of evolutionary-conserved inflammatory mediators: Free radicals, NO, proinflammatory cytokines (IL-1, IL-6, TNFα), propiomelanocortin-derived peptides (ACTH, β-endorphin, α-MSH), (cortisol, biogenic amines (noradrenaline, adrenaline, dopamine), & neuropeptides (CRH)

Global reduction in coping strategies with increased antigen exposures (allostatic load!) $\rightarrow$ proinflammatory status

First hit + absence of robust genes $\rightarrow$ vulnerability to specific diseases i.e., Alzheimer’s, DM2, CA

Positive role for lifestyle, diet, positive epigenetic stimulus and removal of harmful stimuli in promoting longevity and genetic robustness
Thyroid Impact

- Down regulation of T3 production
- Increased rT3
How Do We Break the Stress Cycle?
Reframe & Reset

• Reframe Hormesis & Perceptions of Stress
• Introduce patients to concepts of resilience & self-efficacy
• Tend and Befriend
• Discuss & emphasize supportive lifestyle changes/stress reduction tools
  – Blood sugar balance
  – Sleep support/Sleep hygiene
  – Life coaching
• Nutritional supplements
• Adaptogens
Adaptogens: What Are They?

Primary class of herbs used to support and restore HPA axis function

To be considered an adaptogen, the substance must demonstrate/be:

• Non-specific effects in that the adaptogen increases resistance to a broad spectrum of stressors of physical, chemical, and biological natures

• Normalizing effect, that is, it counteracts or prevents disturbances brought about by stressors

• Innocuous to the normal functioning of the organism

• “Herbal preparations that increase attention and endurance in fatigue, and reduce stress-induced impairments and disorders related to the neuroendocrine and immune systems.”
Psychoneuroimmuno Benefits

- Energy
- Immunity
- Mood
- Repair
- Sleep
- Stamina
- Focus
Modes of Action: “Amphoteric” Regulation

- Phenolic compounds structural resemblance to catecholamines
- Tetracyclic triterpenes similar to the corticosteroids
- Modulate ACTH & corticosteroid formation; normalize stress hormones, allowing the organism to resist stress at higher levels of challenge
- Regulation of CRH, ACTH, NO, PGE2, LTB4, and corticosteroid secretion
- Limit overproduction of catecholamines via COMT inhibitory action
- Regulation of CNS and immune “on-off” switches → reduction in host susceptibility to damage
- Faster recovery of m-RNA after exhausting exercise; increased protein synthesis
- Increased recovery of leukocyte counts after exposure to chemical stressors
- Energetic regulation during stress via glucose-6-phosphate leading to an insulin-like effect
- Reduction in oxidative stress/lipid peroxidation
Adaptogen Safety

- Generally well tolerated, historically considered very safe
- Precautions, theoretical or based on limited animal and human clinical research include, some possibly "advantageous"
  - Increased BP
  - Decreased BP due to vasorelaxant effects
  - Increased digoxin levels in combination
  - Inhibition of platelet aggregation
  - Blood glucose lowering effects
  - Blood glucose increases post-prandially
  - Caution in patients with autoimmune disorders & post-transplant patients
  - Potential for activation in patients with agitation/sedation
  - Caution w/combined steroid use as ES binds steroid receptors
Adaptogen Safety

• Safety not determined in pregnancy; I personally consider questionable due to
  – Effects on blood sugar
  – Immune regulation
  – Placentation
  – Impact on normal metabolic & immunologic changes in pregnancy

• Undetermined during lactation; likely safe
Intended Duration of Use

• Most studies up to 12 weeks
• Traditionally not limited and may be used for extended durations
• Recent data suggests beneficial effects of single doses and statistically significant benefits off shorter treatment periods vs. long term use
Rhodiola

Traditional Use

- “Asthenic” conditions
- Decline in work performance
- Sleep disturbance
- Poor appetite
- Irritability
- Sexual dysfunction
- Fatigue subsequent to intense physical or intellectual strain or illness
- Headache
Twelve randomized controlled trials were included, all of which were placebo controlled trials.

Six trials evaluated rhodiola for exercise performance, four for mental performance, and two for mental health conditions.

Significant benefit was noted in eight studies.

Adverse effects were mild and infrequent.

Five of the studies had a Jadad score of 3 or higher, indicating good quality.
Rhodiola & Anxiety

Open-label study on effects in the treatment of generalized anxiety disorder (GAD) in 10 patients, men and women, ages 18-64, with a DSM-IV diagnosis of GAD.

- Hamilton Depression Rating Scale (HDRS) scores > 17 and Hamilton Anxiety Rating Scale (HARS) 16 or >
- Patients allowed to take SSRIs, SNRIs and benzodiazepines daily prn
- Rhodax® (Phoenix Laboratories by Bodyonics Ltd.) 340 mg daily for 10 weeks
- Assessments included the HARS, HDRS
- *Rhodiola group found to have significant decreases in mean HARS scores at endpoint (p=0.01), as well as a significant difference in HDRS scores (p=0.001)*
Randomized cross-over trial looking at Rhodiola & Mental Performance/Mental Fatigue

- 56 young, healthy physicians
- Standardized extract of Rhodiola (SHR-5) study of fatigue during night duty
- Treated with SHR-5 (170mg daily) or placebo, followed by a 2 week washout and 2 weeks with the opposite treatment
- During the first two weeks of testing, SHR-5 treatment resulted in significant improvement in the mental performance tests.
Cognitive Stress in Students

RCT with placebo arm Rhodaxon on physical and intellectual working capacity and psychoemotional state of foreign students in their first year of studies

- 60 male Indian students studying in Russia
- 660 mg daily for 20 days
- Treatment group showed a 60.7% (p<0.05) increase in strength of work executed
- Slight improvement in concentration (volume of information reviewed and number of mistakes)
- Only rhodaxon group showed improvement in self-evaluation
- Physical state, activity level, and mood improved by 9.1, 10.8, and 10.5%, respectively
- The rhodaxon group reported a 30% decrease in psychological fatigue, while the control and placebo groups both experienced an increase.
- Readiness to work improved by 74%
- Greater “adaptability” demonstrated
Rhodiola & Exercise Performance

RCT/PC to examine the effect of acute and chronic Rhodiola intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention

- 24 healthy young subjects over two sessions
- 200 mg rhodiola
- Speed of limb movement, aural and visual reaction time, and the ability to sustain attention were assessed 1 hr after administration, crossed over to placebo and endurance tests repeated the next day
- Following a 5-day washout period, the experiment was repeated with the opposite treatment group
- In the second, longer-term study, 12 subjects were included
- Rhodiola vs placebo, 4 weeks, and then crossed over to placebo

- Short-term use of Rhodiola significantly increased time to exhaustion peak compared with placebo
- Longer-term use of Rhodiola lacked effect on any variables
Rhodiola on Exercise Induced Inflammation and Muscle Damage

Randomized, double-blind, placebo trial to evaluate the effects of Rhodiola on CRP and CK

- 36 healthy volunteers, 21-24 yo.
- 340mg of Rhodiola bid 30 days before and 6 days after exhausting physical exercise (intense mechanical bicycling)
- CRP and CK measured 30 minutes before exercise, 5 hours after, and five days after. The increase in CRP following exercise was less pronounced in the rhodiola group five hours after exercise (p<0.05).
- After five days, CRP levels did not change (p<0.05) in the rhodiola group but increased in groups 2 and 3.
- In group 1, CK content decreased and sevenfold surpassed the initial level (p<0.05), while in groups 2 and 3 it increased and 15-fold surpassed the initial level.
- Rhodiola was found to have anti-inflammatory effects and protected muscle tissue during exercise.
RCT/ DB/PCO to evaluate the effects of SHR-5 in the treatment of mild-to-moderate depression

- 89 subjects ages of 18 to 70 participated in the 6 week study.
- Participants with initial scores of $\geq 13$ on the Beck Depression Inventory and $\geq 21$ on the HAMD eligible
- Randomized to one of three groups. Group 1 340mg daily, Group 2 two 680mg daily, and Group 3 two placebo tablets daily.
- Statistically significant differences not reported in the average depression scale scores before the herb extract or placebos were given.
- Post treatment, both groups given SHR-5 experienced statistically significant declines in total levels of symptoms compared to placebo ($p<0.0001$).
- HAMD scores declined from 24.52 to 15.97 and from 23.79 to 16.7 while the placebo group did not show statistically significant decreases.
- Improvements were also noted in Beck Depression Inventory scores ($p<0.0001$) as well as symptoms of insomnia, emotional instability, and level of somatization.
Randomized, double-blind, placebo controlled, parallel-group study to evaluate SHR-5 in the treatment of chronic fatigue syndrome

- 60 participants aged 20 to 55 years, diagnosed with CFIDS.
- Participants received 576mg of extract daily (N=30) or 4 placebo tablets daily (N=30).
- QOL (SF-36 questionnaire), symptoms of fatigue (Pines' burnout scale), depression (Montgomery-Asberg depression rating scale-MADRS), attention (Conners' computerized continuous performance test II; CCPT II), and saliva cortisol response to awakening were assessed on days 1 and 28 after treatment.
- Compared to placebo, significant effects of rhodiola were observed in Pines' burnout scale and the CCPT II indices omissions, Hit RT SE, and variability.
- Pre- vs. post-treatment cortisol responses to awakening stress were significantly different in the rhodiola group compared to placebo.
- Adverse effects were not noted.
Rhodiola & Fertility

- Forty women suffering from amenorrhea
- 100 mg of Rhodiola twice daily for 2 weeks or an injection for 10 days
- In some women, the regimen was repeated 2-4 times
- Normal menses were restored in 25 women, 11 of whom became pregnant
Rhodiola Safety & Dosing

Safety

• Very low level of toxicity in animal studies.
• The toxic dose for humans is calculated to be about 235,000 mg; the typical daily dose for chronic problems is 360-600 mg per day when standardized for 1% rosavín, 180-300 mg when standardized for 2% rosavín, or 100-170 mg when standardized for 2.6% rosavín.
• May be activating in some individuals, not recommended for patients with BPAD

Dose

• Clinical trials use products containing 2-3% rosavín and 0.8-1% salidroside
• Dose 100 mg-400 mg/day
Eleutherococcus (ES)

**Traditional Use**

- Increased endurance
- Memory improvement
- Immunological enhancement
- Overall well-being

Farnsworth et al review of Russian clinical trials on > 2,100 healthy human subjects, ranging in age from 19-72 yo indicates increased ability to accommodate to adverse physical conditions, improvement in mental performance, and enhancement of the quality of work under stress.
ES & HSV-2

A specific ES extract, standardized to contain eleutheroside 0.3% (Elagen), orally seems to reduce the frequency, severity, and duration of herpes simplex type II infections.

- In a double-blind study to examine the effect of ES extract on symptoms of genital herpes in 93 men and women, a pure standardized extract of ES was used.
- After 3 months patients using the ES extract reported a reduction in severity, duration, and frequency of outbreaks compared with placebo.

ES & Common Cold

- A specific combination product containing ES plus andrographis (Kan Jang, Swedish Herbal Institute) orally significantly improves symptoms of the common cold when started within 72 hours of symptom onset.
- Some symptoms can improve after 2 days of treatment. It typically takes 4-5 days of treatment before there is maximal symptom relief.
- The combination of ES and andrographis relieves cold symptoms better than Echinacea or placebo in children.
Forty-six patients in the pilot study and 179 patients in the phase III study completed the study. Medication was taken tid for a minimum of 3 days and a maximum of 8 days for the pilot study, and for 3 days in the phase III study. Primary outcome measures were related to pain in the muscle, cough, throat symptoms, headache, nasal symptoms, eye symptoms, and temperature. The physician’s fixed-score diagnosis was based on ear, nose, oral cavity, lymph gland, tonsil, and eye symptoms. The total symptom score showed a tendency toward improvement in the pilot study (p=0.08), while both the total symptom score and total diagnosis score showed highly significant improvement (p≤0.0006 and 0.003, respectively) compared with the placebo group. In both studies, throat symptoms showed the most significant improvement.
**ESES & Influenza**

Kulichenko et al. conducted a randomized controlled study comparing Kan Jang® (a combination product containing ES) vs. amantadine in the treatment of influenza.

- 540 patients enrolled in the first phase of the study; the second phase enrolled 66 patients.
- Outcomes were the duration of sick leave and frequency of post-influenza complications.
- *Kan Jang® contributed to quicker recovery and reduced the risk of post-influenza complications.*
- *Kan Jang® was well tolerated by patients.*

**ES & General Immunity**

Bohn et al. conducted a placebo controlled study to examine the effect of a ES extract (Eleu-kokk®) on immune system function in 36 healthy volunteers.

- Volunteers received 10mL of an ethanolic extract of ES or placebo (wine) three times daily for four weeks.
- The main endpoint was cellular immune status, as determined by quantitative flow cytometry.
- *ES use resulted in an increase in the absolute number of immunocompetent cells, mainly T helper cells. There were also effects on cytotoxic and natural killer cells.*
- There were no side effects observed over a six-month period.
AIF is a water-soluble extract of Panax notoginseng, Rehmannia glutinosa, and ES.

Fifty-seven patients with knee OA, from 43 to 73 years of age, who fulfilled the American College of Rheumatology classification of idiopathic osteoarthritis of knee with radiographic criteria

Randomized to receive two capsules of 400mg of AIF or similar identical placebo twice daily for six weeks.

Outcome measures included pain intensity using a visual analog scale, as well as changes in the Korean version of the Western Ontario and McMaster Universities (K-WOMAC) index score.

Pain was significantly reduced (at visit 2: 54.64 ± 14.72, at visit 4: 37.32 ± 16.58, p<0.001) after AIF administration.

There was an improvement in the physical function of K-WOMAC scale that was significantly higher in the AIF group (p=0.013). Decreases of total K-WOMAC score were also significantly higher in the AIF group (p=0.030).

No serious adverse effects observed.
ES & Exercise Performance

- Traditionally used as an exercise performance enhancement agent, due to its supposed beneficial effects on cardiorespiratory fitness, fat metabolism, and performance endurance
- More effective than placebo in two clinical trials. In four human trials, not more effective than placebo
- More effective than Chinese ginseng

RCT equivalence study to compare the effects of ES with that of echinacea on physical fitness.

- 50 healthy volunteers, male and female, 21-73 years of age
- Subjects randomly divided into two groups: ES root extract or echinacea for 30 days.
- Of these study subjects, 20 healthy males underwent an ergospirometric study.
- Following use of ES, there was a higher oxygen plateau, indicating increased oxygen consumption during maximal physical exercise.
- There was an increase in aerobic metabolism of tissues. In the ES group, there was an increase in cellular immunity as determined by an increase in the rate of blastic transformation of lymphocytes in the presence of mitogen and the phagocytic activity of neutrocytes.
- Total cholesterol, LDL cholesterol, and free fatty acids were all reduced in the ES group. There was a significant reduction in triglyceride levels and glucose found in the ES group.
McNaughton et al. compared the effects of ES and Chinese ginseng with placebo on exercise tolerance in a randomized crossover study.

- Thirty trained runners were included and assigned to ES (1g daily), Chinese ginseng, or placebo, for six weeks each.
- Major endpoints included VO2max, heart rate recovery, and strength. ES had no effect on VO2max, heart rate recovery, or grip strength, compared with the placebo.
- There was a significant increase in pectoral and quadriceps strength, by 15 and 13%, respectively.

Asano et al. conducted a single-blind crossover study to examine the effect of ES on physical working capacity in six healthy male athletes.

- Subjects belonged to the same baseball team and ate the same food.
- No other inclusion or exclusion criteria were provided. Subjects were given 2mL of ES extract (150mg of dried material) or placebo twice daily for eight consecutive days.
- The main endpoints were maximal work on a bicycle ergometer and aerobic capacity.
- Total work increased significantly with ES compared with the placebo group (23.3% vs. 7.5%), as did exhaustion time (16.3% vs. 5.4%).
- Maximal oxygen uptake was only increased compared with control (pre-supplementation).
- Limitations to this trial include the single-blind nature of the study and no mention of randomization.
Comparison of the effect of ES to a combination ES, Cordyceps, and ginseng on cardiorespiratory fitness during submaximal cycling exercise

- 16 healthy male volunteers
- Group A (N=8) received 10 mL of oral ES preparation (Endurox®) equivalent to 800 mg of ES daily, 30 minutes before breakfast. Group B (N=8) also received the same dose of Endurox®, in addition to 400 mg of Cordyceps and 200mg of ginseng liquid extract, in the form of an oral liquid preparation.
- 2 week duration of study
- Both groups received placebo medication for three days prior to treatment initiation.
- Subjects completed aerobic and anaerobic exercise tests, once after three days of placebo, and again after two weeks of active treatment.
- Outcome measures included heart rate, lactate accumulation, and respiratory quotient.
- The submaximal cycling test started at an initial load of 60W for three minutes and then increased every three minutes by 30W, up to 210W.
- **Following ES supplementation, both heart rate and lactate accumulation decreased (34%, in group A), load increased (12% in group A), VO2 at anaerobic threshold) increased (7%, in group A), and fat metabolism increased (43%).**
- **ES supplementation alone was more effective than the combination with Cordyceps and ginseng.**
Forty healthy females (20-68 years of age) that reported living under chronically psychologically stressful conditions participated. The participants were randomized into to receive a single tablet of 270 mg of ADAPT-232 (N=20) or a single tablet of placebo (N=20)

- A Stroop color-word test was used to exhaust the volunteers before the assessment of cognitive function of patients. The effects of ADAPT-232 extract were measured prior to treatment and two hours after treatment using the d2 test of attention (d2)
- The subjects in the ADAPT-232 group quickly gained improved attention and increased speed and accuracy during stressful cognitive tasks, in comparison to placebo (p<0.05)
- There was a tendency of ADAPT-232 to reduce percentage of errors
- A few minor adverse events, such as sleepiness and cold extremities, were observed in both groups. The effects of ES alone cannot be determined from this study
RCT to Examine the Effect of ES for Chronic Fatigue Syndrome

- Subjects were required to have substantial fatigue for 6 months or more, with no identifiable cause.
- Patients with HTN and certain medications, diseases, and abnormal laboratory results were excluded.
- 96 subjects (~80% female) were included, and 76 patients completed the study. The remaining patients were lost to follow-up or to side effects, such as nervousness, headache, and breast tenderness.
- Patients were given placebo or four 500mg capsules of ES (Frontier Herbs, Norway, IA) for 2 months.
- Main endpoint: mean change in a fatigue measure, compared with placebo, at one and two months.
  - *Fatigue was reduced in study subjects overall, with no differences between groups.*
  - *In patients with less severe fatigue, fatigue severity and duration were reduced in those taking ES*
Other Interesting ES Data

Neurocirculatory Hypotension
(i.e., Potts Syndrome, Autonomic Dysfunction)

• Preliminary data suggest that use of ES extract increases systolic and diastolic blood pressure in individuals with neurocirculatory hypotension

• Kaloeva examined the efficacy of ES extract on neurocirculatory hypotension in children aged 7-10 years. Systolic and diastolic blood pressures were increased with treatment
ES Safety & Dosing

Safety
• According to a review, side effects of ES are considered to be minimal
• Root extract has been used safely in clinical trials lasting up to 2 months
• A specific combination product containing ES plus andrographis (Kan Jang, Swedish Herbal Institute) has also been safely used in multiple short-term clinical trials lasting 4-7 days
• One clinical trial used this combination (with andrographis) product in low doses for up to 3 months

Dosing
• Powder: 400 mg bid-tid
• Tincture (1:4) 60-100 drops 3-4 times daily or a fluid extract (1:1) 20-40 drops three times daily has been use
• Variably standardized to eleutherosides B and E
Ashwagandha

Traditional Use

• *Rasayana* herb in Ayurveda
  – Increased vitality
  – Longevity
  – Prevent disease
  – Relieve fatigue, nervous exhaustion, anxiety
  – Insomnia
  – Memory-enhancing
  – Retard “brain aging”
  – Regenerate neural tissue
  – Arthritis
  – GI disorders
Anxiety

RCT studying ashwagandha in a combination naturopathic care model for anxiety treatment (N=81) in subjects with moderate-to-severe anxiety lasting six weeks or longer

- Treatment was composed of dietary counseling, deep breathing exercises, a multivitamin, and ashwagandha root 300mg twice daily (standardized to 1.5% anolides) for 12 weeks vs. control therapy without ashwagandha

- Beck Anxiety Inventory scores decreased 56.5% from baseline (p<0.0001) in the treatment group and 30.5% (p<0.0001) in the control group

Hypercholesterolemia

A case series including 6 subjects with hypercholesterolemia showed that ashwagandha 3 grams daily for 30 days decreased serum cholesterol, triglycerides, low density lipoproteins (LDL), and very low density lipoproteins (VLDL)
Osteoarthritis

- A specific combination containing ashwagandha 450 mg, zinc complex 50 mg, guggul 100 mg, and turmeric 50 mg (Articulin-F), 2 capsules tid for 3 months improved symptoms in patients with joint deformity, pain, stiffness, and swelling. No radiological improvements were seen after treatment.
- 32 week RCT of 90 patients with OA of knee found extract containing ASH, boswellia, ginger, and tumeric was superior to placebo for relieving pain & improving function.

Diabetes

A case series including 6 subjects with type 2 diabetes showed that ashwagandha 3 grams daily for 30 days decreased blood glucose to a degree similar to oral hypoglycemic drugs; however, it wasn’t specifically compared to oral hypoglycemic drugs.
Enhanced Immunity

- Combination Ayurvedic herbal tea increased NK cell activity (N=32). *Elettaria cardamomum, Glycyrrhiza glabra, Ocimum sanctum, Withania somnifera,* and *Zingiber officinale* were compared to regular tea in healthy volunteers aged ≥55 years with low baseline NK cell activity and recurring coughs and colds.

- 6mL of ashwagandha root extract with whole milk twice daily for 96 increased CD4, CD8, CD19, CD56, and CD69 receptor cell surface expression and increased CD4 expression on CD3+ T cells after 96 hours. CD56+ NK cells were also activated. (N=5)
Safety

- Used safely in clinical trials lasting up to 12 weeks.
- Orally, well tolerated at typical doses.
- Large doses may cause GI upset and vomiting secondary to irritation of the mucous membranes.
- While pregnancy abortifacient activity found in some literature it is based on erroneous reporting of a single case history, safety during pregnancy is not conclusive though there is evidence of traditional use.
- Theoretical condition or drug interactions: CNS additive effects, antihypertensive effects, thyroid stimulating effects, aggravation of PUD, reduction in blood glucose levels.

Dose

- 1 to 6 grams daily of the whole herb in capsule or tea form in 2-3 divided doses
- Standardized extracts can be taken at 500 mg, 2-3 x/day.
- The tea is prepared by boiling ashwagandha roots in water for 15 minutes and cooled. The usual dose is 3 cups daily.
- Tincture or fluid extracts are dosed 2 to 4 mL 3 times per day.
Additional Support

**Botanical “Nervines”**
- SJW
- Lavender
- Passion flower
- Valerian
- Lemon balm
- California poppy
- Kava kava

**Nutritional Supplements**
- B-complex
- Magnesium
- 5-HTP
- P-S
- Methylfolate
- GABA
- L-tyrosine, L-theanine
- Inositol
Questions?
Additional Education Materials:

WWW.GDX.NET

Sample Reports, Support Guides, Kit Instructions, FAQs, Payment Options, and much more!
Please schedule a complimentary appointment with one of our Medical Education Specialists for questions related to:

- Diagnostic profiles featured in this webinar
- How Genova’s profiles might support patients in your clinical practice
- Review a profile that has already been completed on one of your patients

We look forward to hearing from you!
Upcoming LIVE GDX Webinar Topics

August 2016

– Weight Management: Hormonal Imbalance and Nutritional Insufficiencies
  • Melanie Dorian, NP

Register for upcoming LIVE GDX Webinars online at WWW.GDX.NET

The views and opinions expressed herein are solely those of the presenter and do not necessarily represent those of Genova Diagnostics. Thus, Genova Diagnostics does not accept liability for consequences of any actions taken on the basis of the information provided.
The Stress Response, Women’s Health & the Role of Adaptogens

Aviva Romm, MD

The views and opinions expressed herein are solely those of the presenter and do not necessarily represent those of Genova Diagnostics. Thus, Genova Diagnostics does not accept liability for consequences of any actions taken on the basis of the information provided.
References

Slide 2

Slide 3

Slide 4

Slide 5

Slide 6

Slide 7


Slide 8


Slide 9


Slide 10

Slide 11


**Slide 12**

**Slide 13**

Johansson, L. et. al. Midlife personality and risk of Alzheimer disease and distress A 38-year follow-up. Published online before print October 1, 2014, Neurology.

**Slide 14**

**Slide 15**

**Slide 18**


**Slide 19**

Slide 20


Slide 21

Slide 23

Slide 24

Slide 25

Slide 26

Slide 27
Slide 28

Slide 29

Slide 30

Slide 31

Slide 32

Slide 33
Slide 34

Slide 35

Slide 36

Slide 37

Slide 38
Slide 39

Slide 40

Slide 41

Slide 42

Slide 43

Slide 44

Slide 45

Slide 45


Rhodiola Mechanisms


ES Mechanisms


