Understanding the Neuroendocrine System:

The key to achieving restorative sleep, hormone balance and stress resilience

Christopher Mote, DO

April 2024

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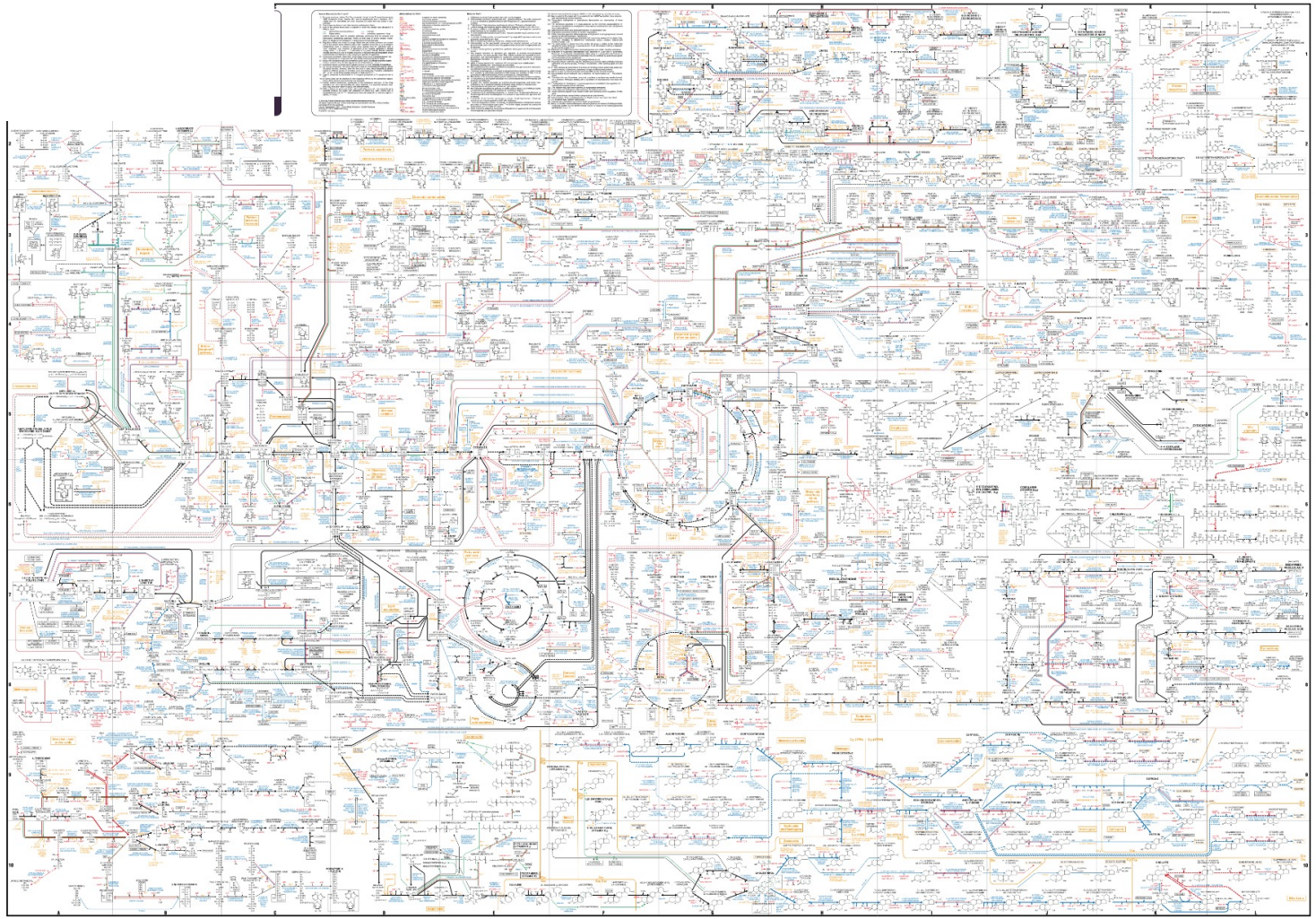
Metabolic Pathways of Human Cell



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Hormone Control Mechanisms: Induction & Production

- Limbic Activation
- Negative Feedback Loops
- Immune and Inflammatory Influences

Hormone Control Mechanisms: Downstream Effects & Metabolism

- Cellular elimination
  - COMT (Gemomics)
  - Cytochrome P450 enzymes (drugs that inhibit, especially tramadol, beta-blockers, paroxetine…)
  - Nutrients: Magnesium, SAMe

- Conjugated hormones eliminated in urine more than stool
  - Estrogens
    - eGFR and Cystatin-C (serum testing)
    - Beta-glucuronidase – microbiome-prebiotics (GI Effects)
    - Stool volume-fiber-pathogens (Hx, H.pylori, etc)
  - Testosterone and Progesterone
    - Glucuronide/ and sulfate conjugates eliminate 90% in urine, small amount in feces

- Cortisol
  - Glucuronic conjugation and excreted in urine

Are we Maximizing Function or Treating Biomarkers?

Reference Range Information

Serum Analyte	Premenopause Luteal	Unsupplemented Menopause	Unsupplemented Male	Patient Result
Estrone (pg/mL)	43 - 250	18 - 63	46 - 143	117
Estradiol (pg/mL)	37 - 246	<15 - 25	<15 - 32	37
Estriol (pg/mL)	<=80	<=80	<=80	<80
Progesterone (ng/mL)	1.21 - 19.47	<=0.78	<=2.06	1.52
Testosterone (ng/mL)	<0.10 - 0.75	<0.10 - 0.75	1.75 - 7.81	0.46
Sex Hormone Binding Globulin (nmol/L)	18.2 - 135.5	16.8 - 125.2	13.3 - 89.5	64.3
Free Androgen Index	0.43 - 8.48	0.32 - 6.73	N/A	2.48

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So where should we start?

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Evolution of Understanding:

- Sex hormones in saliva to assess free fraction (bio available)
- Ran first salivary hormone test in 2001 – four-point cortisol with DHEA
- Low DHEA as indicator of pregnenolone steal, the hallmark of chronic stress and adrenal dysfunction (Adrenal Fatigue: The 21st Century Disease, James Wilson, ND)
- Adrenal Fatigue debunked in 2010 with definitive studies showing salivary cortisol is end-product of stress response starting in Hypothalamus – Cortisol Awakening Response correlated with brain biopsies in mouse models

Chronic Stress and the HPA Axis: Clinical Assessment and Therapeutic Considerations

By Thomas G. Guilliams Ph.D. and Lena Edwards M.D. - 2010

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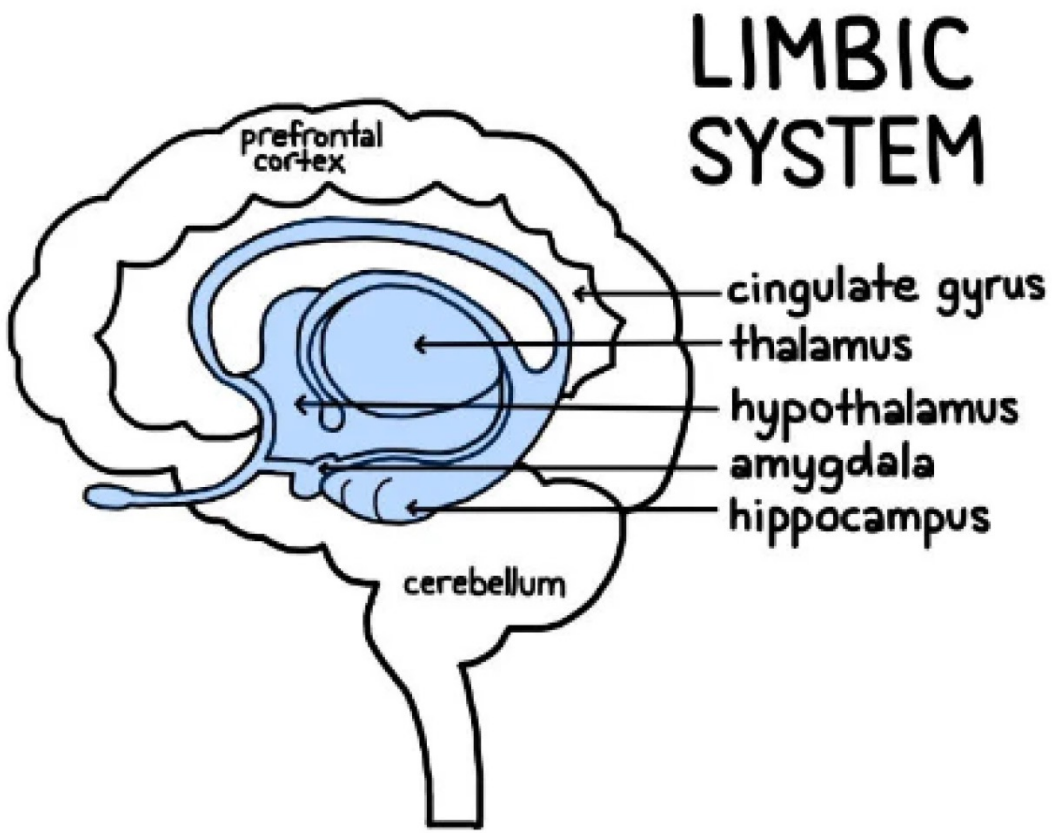
Drivers of HPA Axis:

- Limbic Activation
- Inflammatory Cytokines
- Sleep deficits
- Hypoglycemic episodes

Limbic activation of HPA axis



- Thalamus
- Cingulate Gyrus
- Amygdala
- Hypothalamus
- Hippocampus

Feeling and reacting center

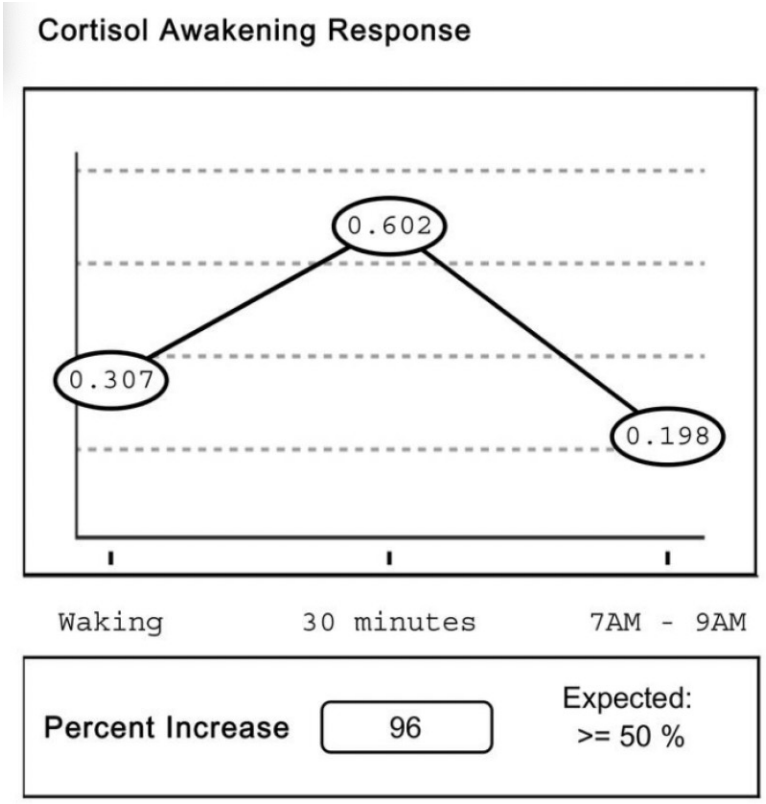
Limbic activation of HPA axis

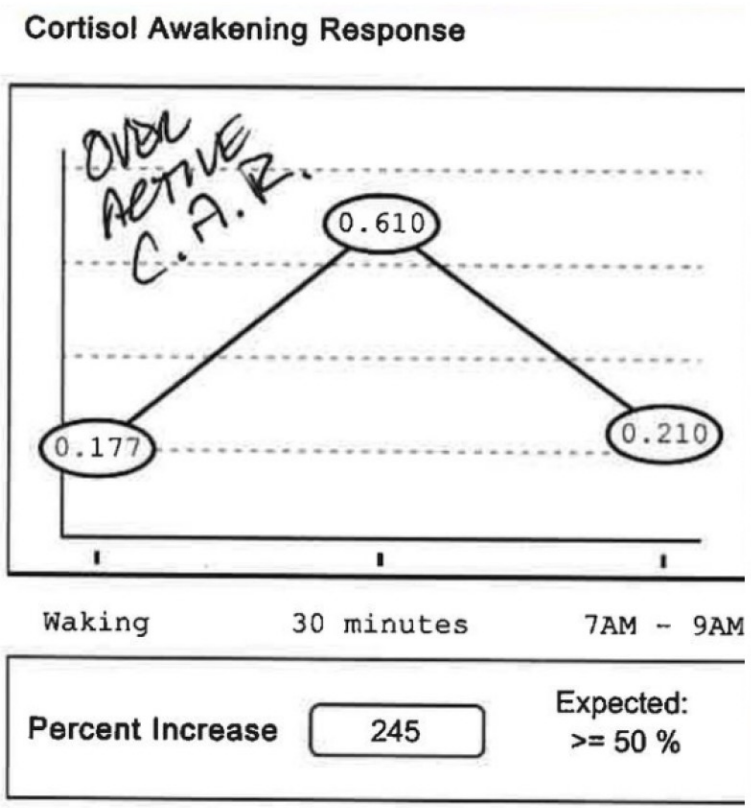
- **Cortisol**
- Adrenaline (SNS – medulla)
- Norepinephrine

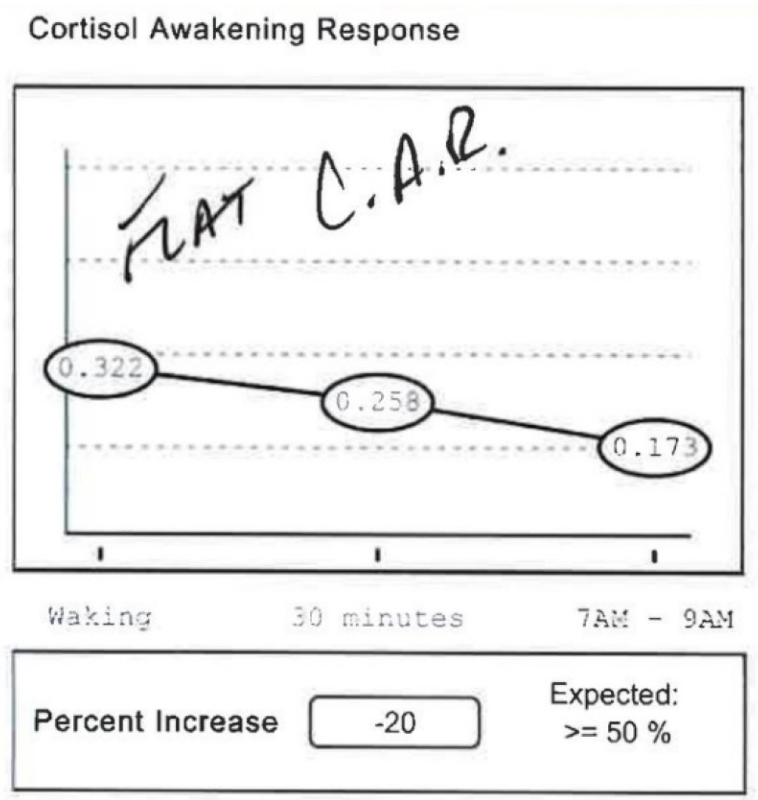
- Also
  - DHEA
  - Aldosterone

- Cortisol Awakening Response (C.A.R.)
- Low Secretory IgA: both fecal, salivary
- Heart Rate Variability (HRV) wearables
- M/C symptoms
  - Anxiety/irritability
  - Brain fog/poor concentration
  - Chronic pain
  - Poor sleep
  - HTN especially due to episodic anxiety/stress

Cortisol Awakening Response:



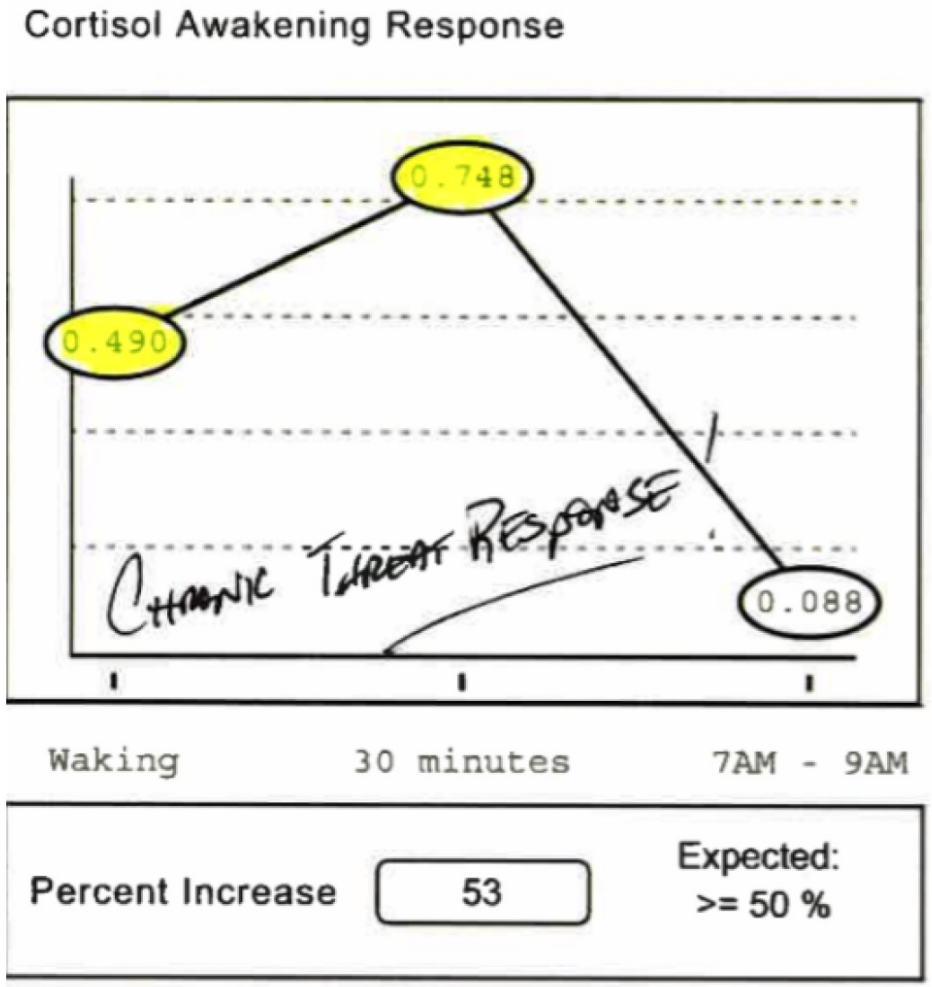




Limbic Activation

- Causes include:

1. Physical or Emotional Injury
2. Toxins or Infections
3. Pervasive Psychological stress



Limbic Interventions:

- **Limbic Retraining Programs: DNRS/Hopper, Gupta Program**

- **Stellate Ganglion Block (SGB): The Stella Center**

- Propranolol/Nadolol: 10-20mg two to three times daily (beta adrenergic blockers)
- GABA, L-theonine, Huperzine, 5-HTP
- Vagal nerve stimulation
- Meditation
- Breathing and other stress techniques

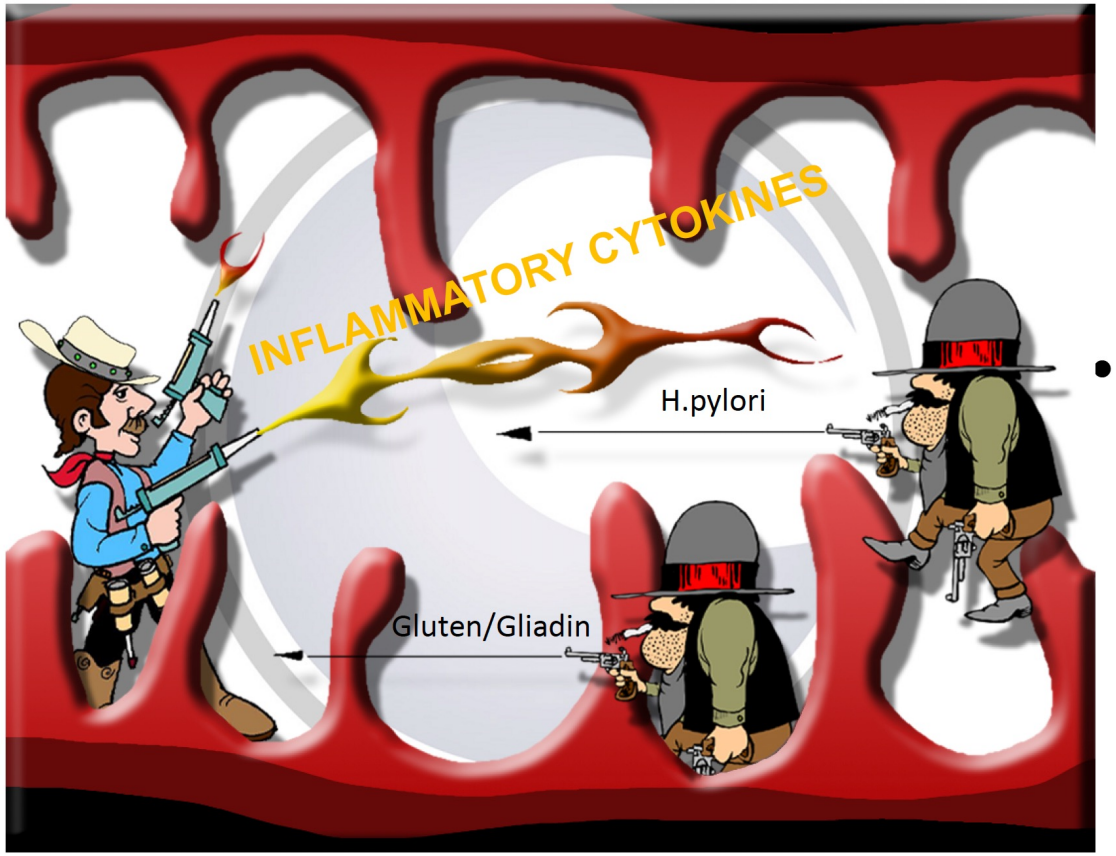
Inflammation as a stress

- Increased antigen load due to increased mucosal permeability
  - Biotoxins: H.pylori, fungal, parasitic, SIBO
  - Delayed food allergens
  - Overtraining (increases in TNF alpha and IL-1beta)
- Cytokine activation:
  - IL-6, TNF alpha with urease and aflatoxins
  - IL-2, IL-5 with ochratoxins
  - IL-8, IL-1a, IL-2, TNF alpha with parasites (B.hominis, E.histolytica, C. parvuum)

Inflammatory response drives limbic activation further hypersensitizing stress response – inflammation driving limbic activation

Inflammation/Infection as a Stress

- Foods
  - Gluten/gliadin
  - Glyphosate
  - Soy Proteins
- Infections/biotoxins (Elevated SIgA)
  - H.pylori
  - Mold/mycotoxins
  - Oral/dental
  - MARCoNs/nasal



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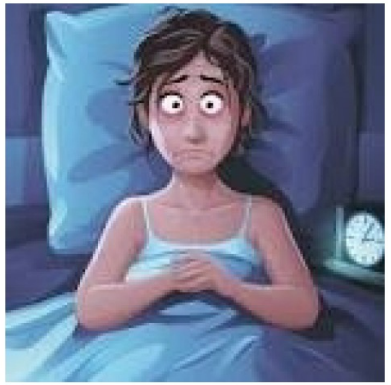
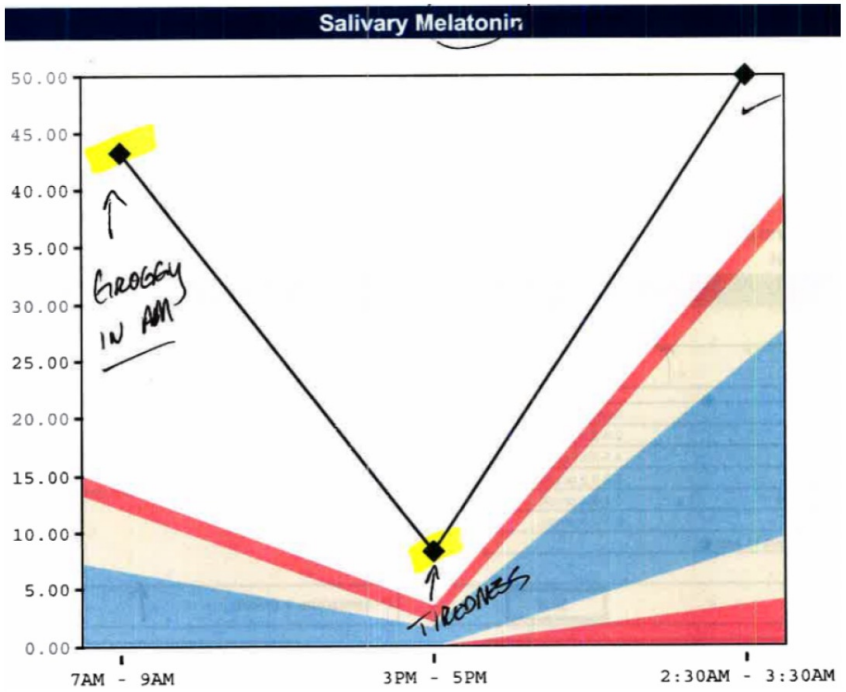
Inflammation Interventions:

- Avoid **gluten, gliadin** (oats and millet) as well as soy proteins
- PCR stool testing for **H.pylori**
- PCR stool and Microscopic O&P for **parasites**
- Stool culture for b**acterial and yeast** overgrowth
- Nasal culture to identify colonization of **MARCoNS and Fungal** along with biofilm
- Cone Beam CT to identify **apical periodontitis** in older root canals

HPA axis activation disrupts sleep



- Cortisol blocks release of growth hormone reducing DEEP/Slow Wave and REM sleep
  - Elevated Bedtime Cortisol (m/c finding)
    - blue light wave length
    - limbic activation with elevated CAR
  - Low Progesterone
    - GABA receptors closed



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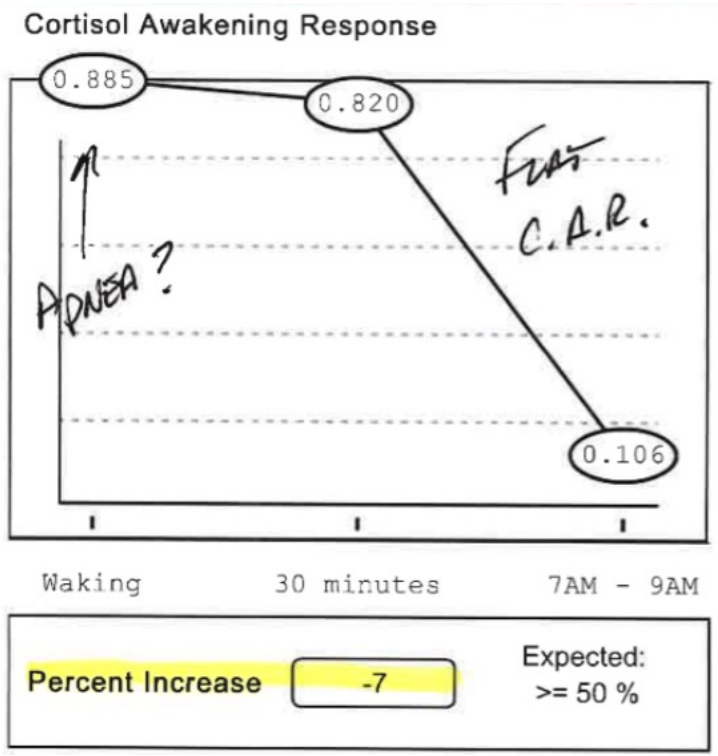
Poor sleep induces HPA activation

- Apnea and sleep deprivation increase cortisol



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Sleep Interventions:

- Phosphatidylserine: 100-300mg at 6pm and again just before bed to lower cortisol (DEEP)
- Melatonin: 1-5mg swallowed at bedtime for delayed effect if low in melatonin at 3am (REM)
- Progesterone: 100mg oral micronized before bed to open GABA receptors and quiet mind (DEEP)
- Magnesium Threonate: 150mg elemental magnesium, before bed to increase GABA (DEEP)
- L-theonine: 200mg before bed to increase Alpha Wave activity (DEEP)
- Circadian rhythm disruption: 20-30min outdoor light with 90 min of blue light blocking before bed
- Sauna, hot tub or bath before bed to calm limbic activation
- If sedentary, increase activity to 30 min of walking, yoga, resistance training 3 times weekly

Hypoglycemia as a Stress

- Hypoglycemic episodes
  - Triggers stress response in HPA axis
  - Resulting in cortisol, epinephrine and glucagon
  - Sympathetic response increased by sensitizing the limbic system
- Hyperglycemic episodes
  - High sugar diet
  - Alcohol
  - Uncontrolled diabetes

- INTERVENTIONS:
  - Increase protein to 0.5g/pound of body weight
  - Eat first meal at same time each day to train circadian rhythm of digestion
  - Eat within 2hr of arising to break catabolism
  - Stop eating 2hr before bed for best DEEP sleep
  - AM drink: flaxseed flour, gaur gum, inulin, glucomannan, ALA, Vanadyl Sulfate

Drivers of HPA Axis:

Limbic Activation

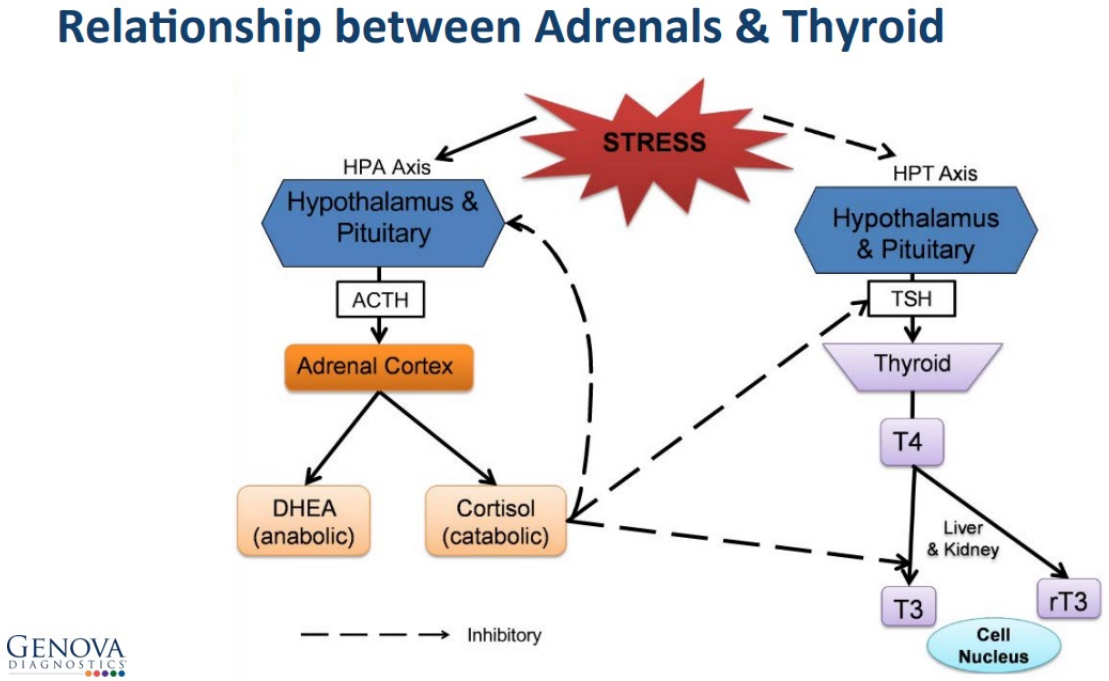
Inflammatory Cytokines

Sleep deficits

Hypoglycemic/Hyperglycemic Episodes

Thyroid changes with HPA axis activation

- Cortisol is catabolic
- In-built “brake” on thyroid and metabolism
- Cortisol lowers TSH and T4 to T3 conversion



Sex Hormone Changes with HPA axis Activation

Increased HPA axis activation:

- Lowers free progesterone
- Lowers free testosterone
- Lowers free estradiol
- Increases Sex Hormone Binding Globulin (with excessive cortisol states)

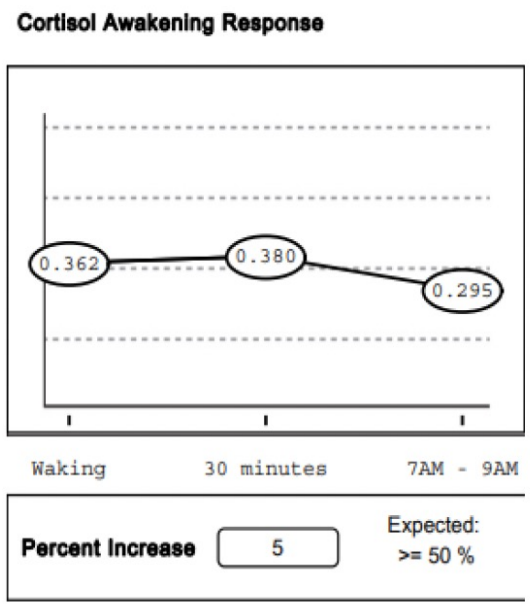
Sex Hormone effects on HPA axis

- Estradiol – increases HPA axis activation by impaired negative feedback
- Progesterone –
  - decreases HPA axis activation (GABA receptors?)
  - provides substrate for cortisol production
- Testosterone – suppressed with HPA activation, low testosterone sensitizes HPA axis

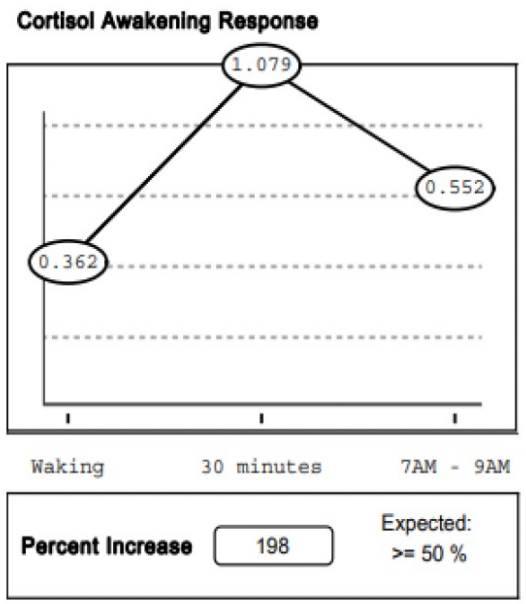
Case Study

- Melissa 55 yo f – C.A.R.

August 2022



December 2022



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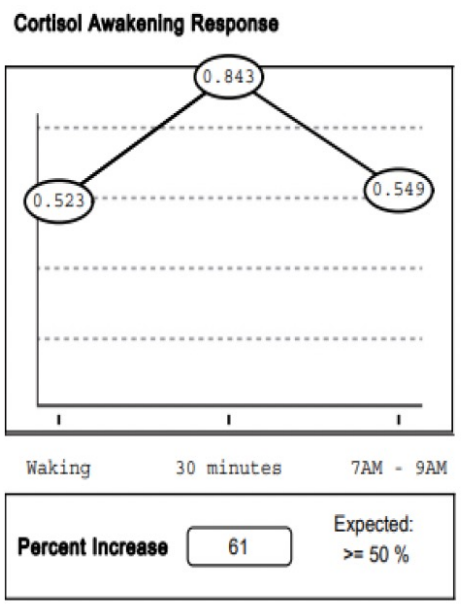
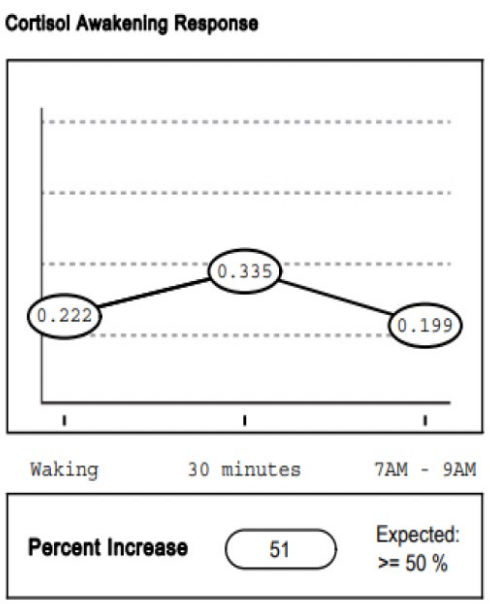


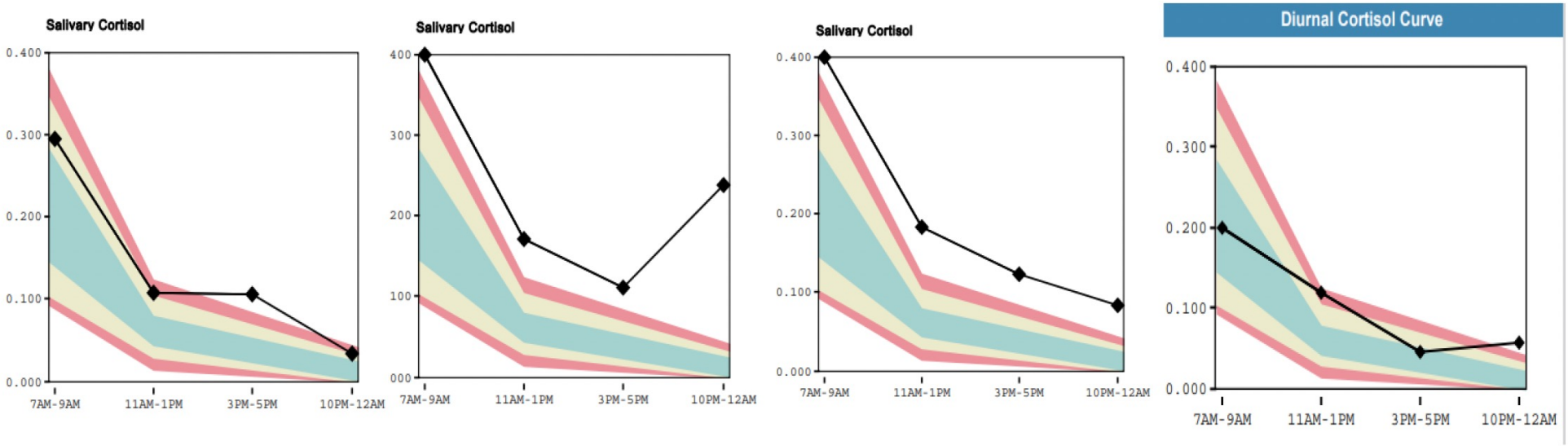
February 2024



Case Study

- Melissa 55 yo f – Diurnal Rhythm

August 2022 December 2022 April 2023 February 2024



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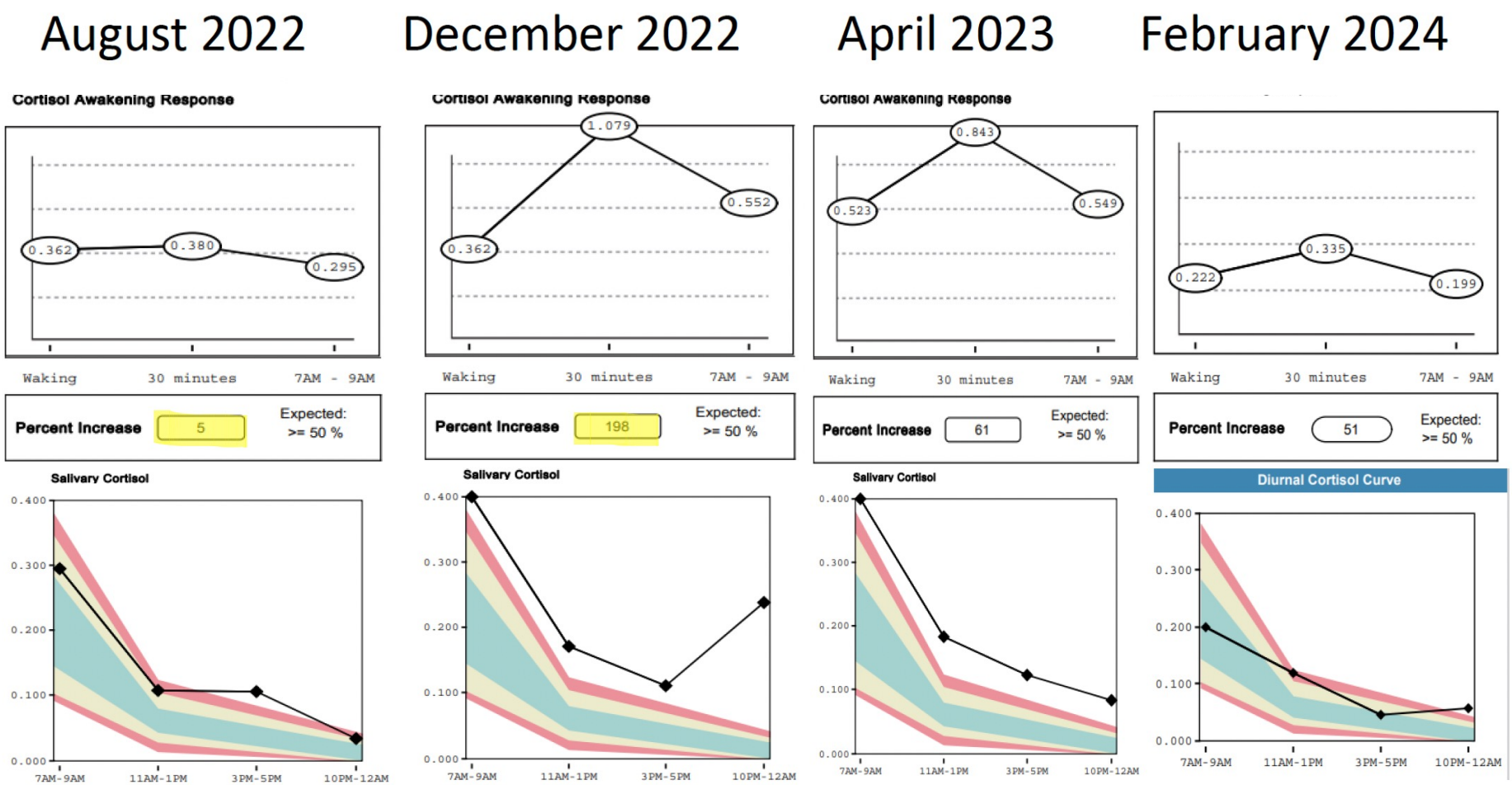

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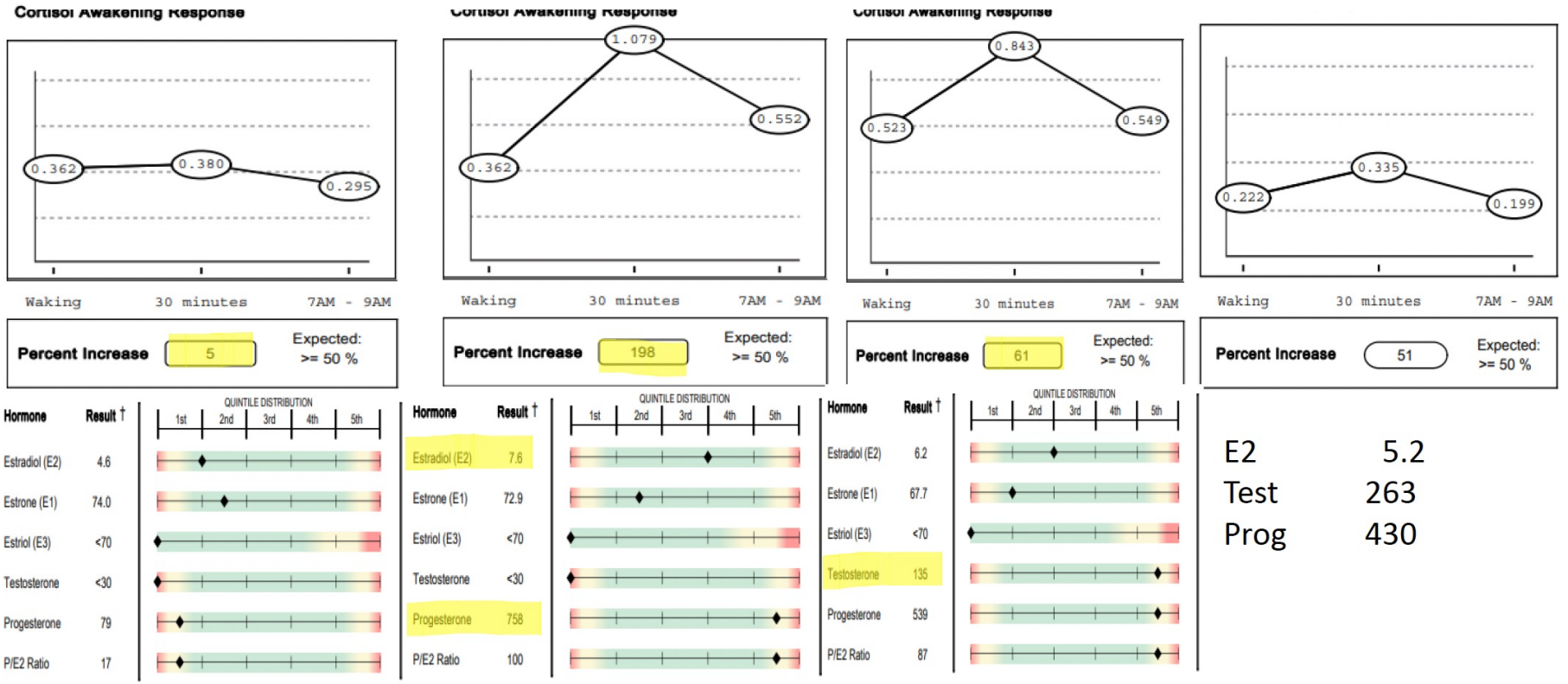
August 2022 | December 2022 | April 2023 | February 2024



E2	5.2
Test	263
Prog	430

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Sex Hormone Balance – ENDO+

- Begin with limbic activation and glycemic control
  - CAR, low Secretory IgA, elevated diurnal cortisol
- Achieve sufficient sleep (7.5hr of total and 3.5hr of DEEP/REM)
  - Wearable/tracker
- Inflammation (foods and infections)
  - Avoidance diet and appropriate evaluation for inflammation (gut, nasal, oral)
- Add hormones last (use less with better results)

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