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Depression & the DUTCH Test: A Holistic Assessment

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Speaker

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I’m happy to share my 11+ years of experience working within the hormone lab testing space where I've provided clinical support and guidance to practitioners learning to apply functional endocrinology in their practices. Thank you for joining today!

Medical Disclaimer

The medical information in this lecture is provided as an information resource only, and is not to be used or relied on for any diagnostic or treatment purposes. This lecture contains general information about medical conditions and treatments. The information is not advice and should not be treated as such. This information is not intended to be patient education, does not create any patient-physician relationship, and should not be used as a substitute for professional diagnosis and treatment.

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Agenda

- Depression is a multi-factorial condition
  - Approach should be diverse and individualized
  - Current pharmacotherapies aren't always completely effective
- We will explore the 7 factors in depression as identified on the DUTCH Plus test:
  - Cortisol, the Cortisol Awakening Response, and HPA Stress
  - COMT Phenotype
  - Sex Hormone Imbalances
  - Key Nutritional deficiencies (B6, B12, D)
  - Neuroinflammation
  - Oxidative Stress
  - Gut microbial dysbiosis
- How to build a lifestyle plan from a DUTCH report to increase clinical response in depression

Abbreviations in this Presentation

- Alpha-pregnanediol: a-preg
- Beta-pregnanediol: b-preg
- 2-hydroxyestrone: 2-OH-E1
- 2-Methyoxyestrone: 2-MeO-E1
- 4-hydroxyestrone: 4-OH-E1
- 16-hydroxyestrone: 16-OH-E1
- Brain derived neurotrophic factor: BDNF
- Catechol-o-methyltransferase: COMT
- Central Nervous System: CNS
- Cortisol clearance rate: CCR
- Copper: Cu
- Dopamine Beta Hydroxylase enzyme: DBH
- Dopamine: DA
- Epinephrine: Epi
- Estrogens: Es
- Estradiol: E2
- Estrone: E1
- Homovanillate: HVA
- Hypothalamic-Pituitary-Adrenal: HPA
- Monoamine Oxidase: MAO
- Neurotransmitters: NTs
- Norepinephrine: NE
- Phenylethanolamine N-methyltransferase: PNMT
- Postmenopausal: PMP
- Premenopausal: PreMP
- Premenstrual Dysphoric Disorder: PMDD
- Progesterone: PG
- Serotonin: 5-HT
- Sympathetic Nervous System: SNS
- Testosterone: T
- Vanilmandelate: VMA

Depression is in Your Office (and Everywhere!)

- Persistent low mood and loss of interest in activities
  - Mild vs Moderate vs Major depends on the degree to which it impacts daily function and relationships.
  - It can be acute, chronic, and/or recurrent.
- Highly prevalent worldwide – 280 million people
- By 2030 will be the leading contributor to global disease burden

Chan VKY, et al. Projecting the 10-year costs of care and mortality burden of depression until 2032: a Markov modelling study developed from real-world data. Lancet Reg Health West Pac. 2024;45:101026.

Common Current Therapeutics in Depression

- Psychotherapy
  - Example: Cognitive Behavorial Therapy
- SSRIs (most commonly prescribed therapeutics for depression)
  - Examples: Citalopram, Escitalopram, paroxetine, fluoxetine, etc
- SNRIs and Atypicals
  - Examples: Venlafaxine, mirtazapine, amitryptiline, etc
- MAOis (less commonly prescribed due to side effect profiles)
- Glutamate/GABA drugs are a newer approach
  - Brexanolone, dextromethorphan-bupropion, esketamine, ketamine

Medications Response rates, Long Term Use, and Side Effect Profiles

- Response rate to first line monotherapy for depression around 50%
- Many patients use anti-depressants in perpetuity but few studies examine use beyond a couple of years
- Side effect profiles can include:
  - GI bleeds
  - Osteoporosis with long term use
  - Sexual side effects/Hypoactive sexual desire
  - Suicidality
  - Weight gain
- Non-Adherence rates sit a little higher than 40%
  - Top reasons in the US: Forgetting to take, belief that it's not needed, and concerns about safety

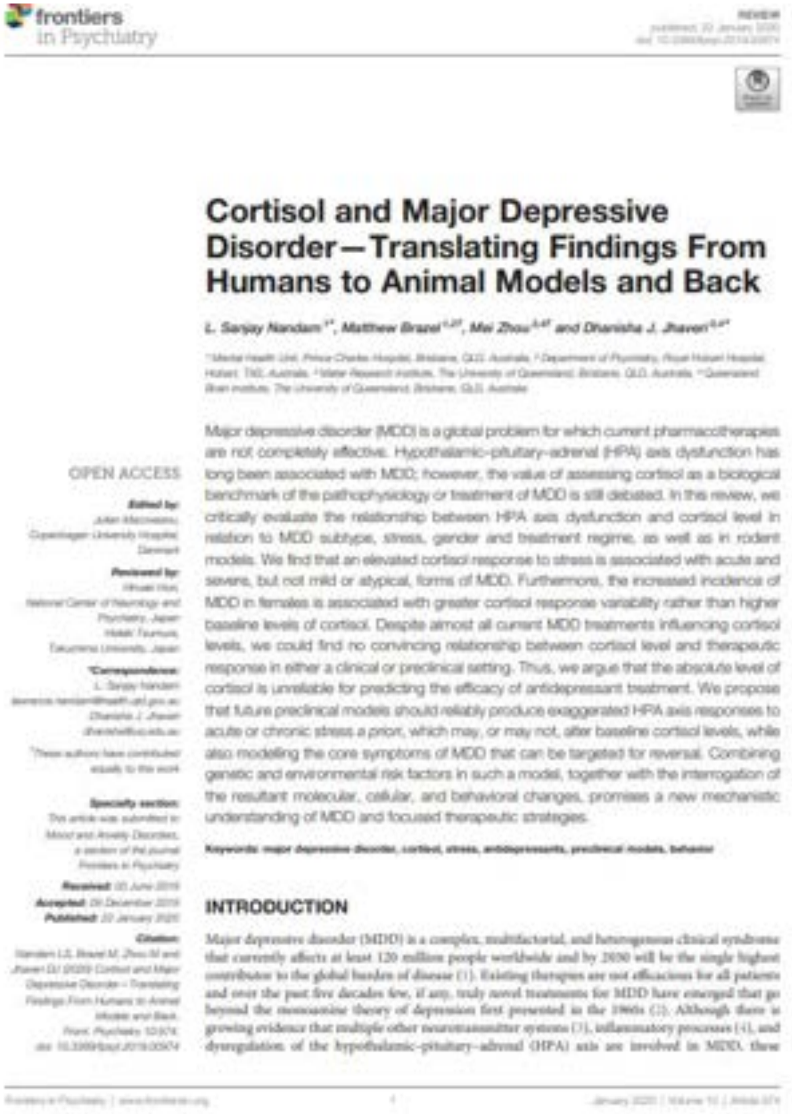
Many Don't Respond to Treatment

- Treatment Resistant Depression affects approximately 30% of patients (in research settings) but is reported as high as 50% in primary care settings.

McIntyre RS, et al. World Psychiatry. 2023
Unni, EJ, et al. J Affect Disord. Vol 344; 2024.

What else can we do?

Depression Involves Multiple Systems Beyond the Monoamine NTs



frontiers in Psychiatry

REVIEW

Cortisol and Major Depressive Disorder—Translating Findings From Humans to Animal Models and Back

L. Sanjay Nandam, Matthew Brazel, Mei Zhou and Dhanisha J. Jhaveri

OPEN ACCESS

Major depressive disorder (MDD) is a global problem for which current pharmacotherapies are not completely effective. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction has long been associated with MDD; however, the value of assessing cortisol as a biological benchmark of the pathophysiology or treatment of MDD is still debated. In this review, we critically evaluate the relationship between HPA axis dysfunction and cortisol level in relation to MDD subtype, stress, gender and treatment regime, as well as in rodent models. We find that an elevated cortisol response to stress is associated with acute and severe, but not mild or atypical, forms of MDD. Furthermore, the increased incidence of MDD in females is associated with greater cortisol response variability rather than higher baseline levels of cortisol. Despite almost all current MDD treatments influencing cortisol levels, we could find no convincing relationship between cortisol level and therapeutic response in either a clinical or preclinical setting. Thus, we argue that the absolute level of cortisol is unreliable for predicting the efficacy of antidepressant treatment. We propose that future preclinical models should reliably produce exaggerated HPA axis responses to acute or chronic stress a priori, which may, or may not, alter baseline cortisol levels, while also modelling the core symptoms of MDD that can be targeted for reversal. Combining genetic and environmental risk factors in such a model, together with the interrogation of the resultant molecular, cellular, and behavioral changes, promises a new mechanistic understanding of MDD and focused therapeutic strategies.

Keywords: major depressive disorder, cortisol, stress, antidepressants, preclinical models, behavior

INTRODUCTION

Major depressive disorder (MDD) is a complex, multifactorial, and heterogenous clinical syndrome that currently affects at least 120 million people worldwide and by 2030 will be the single highest contributor to the global burden of disease (1). Existing therapies are not efficacious for all patients and over the past five decades few, if any, truly novel treatments for MDD have emerged that go beyond the monoamine theory of depression first presented in the 1960s (2). Although there is growing evidence that multiple other neurotransmitter systems (3), inflammatory processes (4), and dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis are involved in MDD, these

"Major depressive disorder (MDD) is a complex, multifactorial, and heterogenous clinical syndrome that currently affects at least 120 million people worldwide and by 2030 will be the single highest contributor to the global burden of disease (1). Existing therapies are not efficacious for all patients and over the past five decades few, if any, truly novel treatments for MDD have emerged that go beyond the monoamine theory of depression first presented in the 1960s (2). Although there is growing evidence that **multiple other neurotransmitter systems** (3), **inflammatory processes** (4), and **dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis** are involved in MDD, these insights have not yet led to new treatments due to our limited understanding of their molecular mechanisms (5)."

Depression Linked to Inflammatory Markers and the Stress Response System

- Inflammatory Marker signatures can even distinguish subtypes in depression
  - Melancholic – higher IL-6
    - Sleep latency and fatigue as hallmarks
  - Atypical – higher CRP and adipokines
    - Weight gain, increased appetite

- Once we understand there's a connection between Depression, Inflammation, and Stress, we can understand where to look for opportunities to treat.

- Many of the ways the body attempts to adapt and function in the presence of inflammatory and immune stress of depression are visible on a DUTCH Test.

Krenek P, et al. Peripheral Inflammatory Markers in Subtypes and Core Features of Depression: A Systematized Review. Psychopathology. 2023;56(5):403-416.

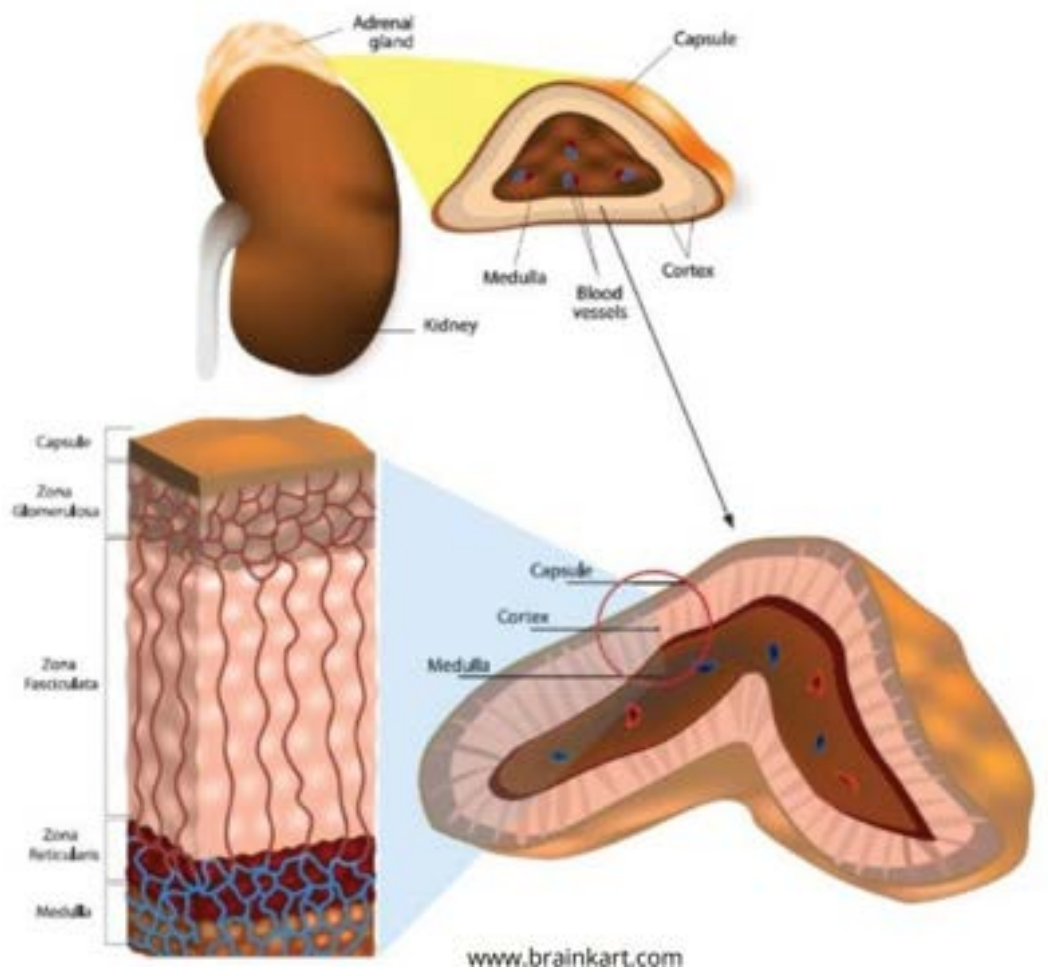
The HPA Axis - Cortisol

Levels
Diurnal Rhythm
Magnitude of Stress Response

The Adrenal Glands Produce Stress Hormones

The Adrenal Glands produce:

- Cortisol
  - Adrenal Cortex: Zona Fasciculata
- DHEA/DHEA-s
  - Adrenal Cortex: Zona Reticularis
- Aldosterone
  - Adrenal Cortex: Zona Glomerulosa
- Catecholamines (Epi and NE)
  - Adrenal Medulla



Exposure to Stress Leads To:

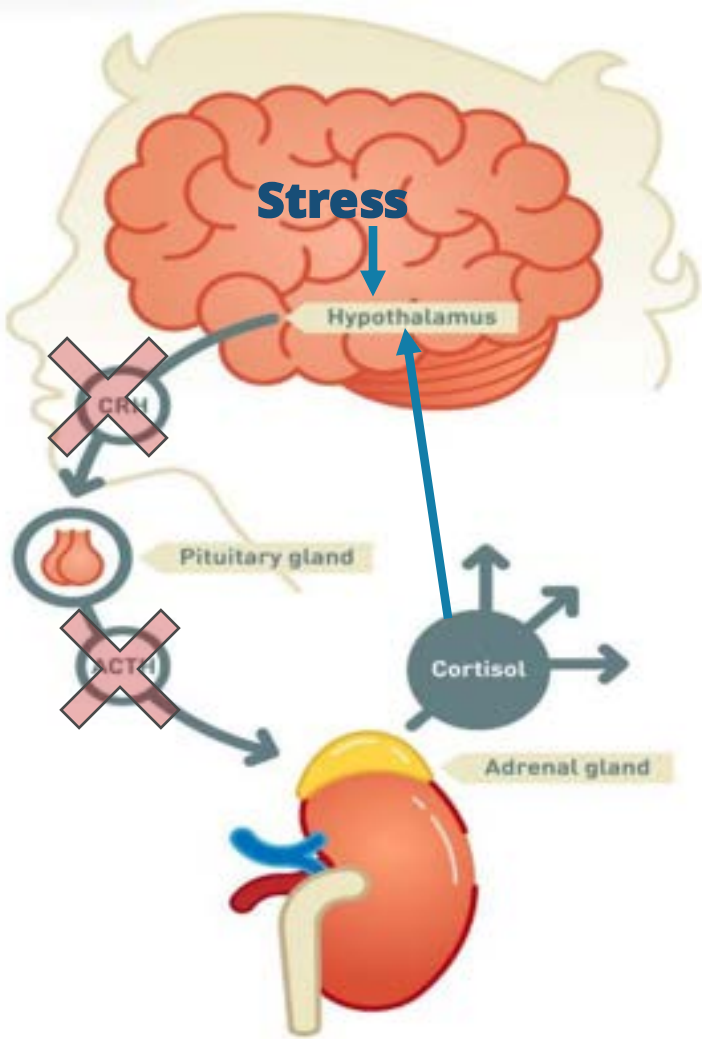
- A Catecholamine Response then a Cortisol Response

- Catecholamines NE and Epi (Adrenal Medulla under CNS Control) – FAST/INITIAL RESPONSE, ENDS QUICKLY
  - Immediate release of stored epinephrine and norepinephrine
  - These are amines the body makes then stores to be at the ready for a threat!
  - This is signaled through the spinal cord via nerve impulses
  - ADRENALINE

- Cortisol (Adrenal Cortex under HPA Axis Control) – SLOWER TO INITIATE, LONGER LASTING
  - The body makes cortisol as needed when signaled by CRH/ACTH – it is not made ahead of time
  - This usually occurs after a stressor signals the BRAIN
  - Lag time is usually about 10 minutes after Epi/Norepi have been released

The Brain (HPA Axis) Governs Cortisol Production Under Stress

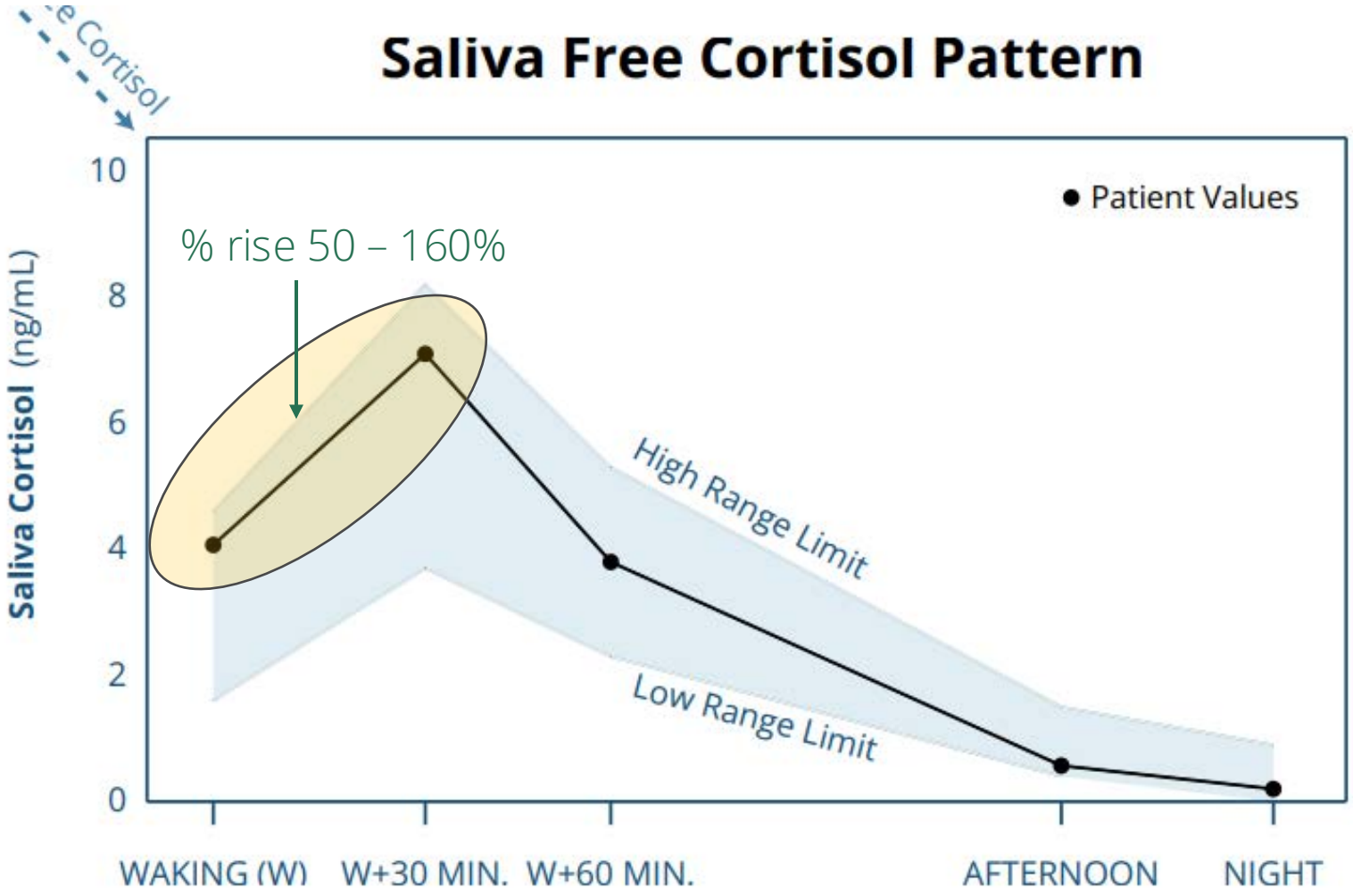
- Acute Stress causes the hypothalamus (H) to make CRH and pituitary (P) to release ACTH which signals cortisol production from the adrenal glands
- Cortisol goes out to tissues to turn on genes to resolve the stressor
- Once stressor is resolved, free cortisol engages its “negative feedback” loop
- Free cortisol binds receptors in the H
- Down-regulates CRH from the H and ACTH from the P
- Cortisol production levels return to baseline



Chronic stress and prolonged HPA axis activation can affect neurotransmitter systems and influence mood and cognition.

Assess HPA axis function using the DUTCH Plus

A Normal Stress Response (CAR) and Diurnal Rhythm of Cortisol

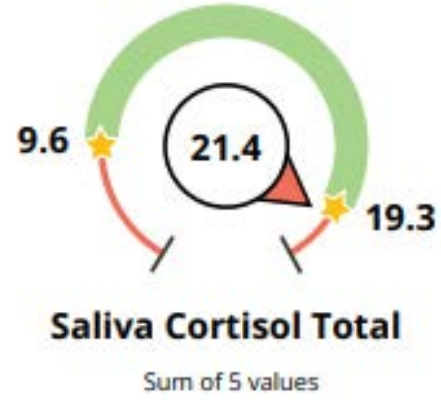


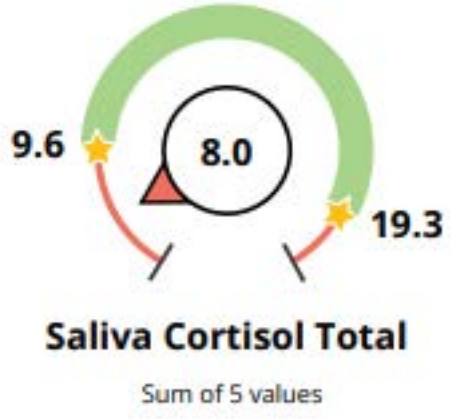
Assess Free Cortisol levels – a Measure of HPA Axis Activity

- Look for abnormalities/highs/lows in cortisol levels, diurnal rhythm, and cortisol awakening response (CAR) – TREAT THERE

- Overall High Cortisol
  - Decreases brain derived neurotrophic factor (BDNF)
  - Damages hippocampus and prefrontal cortex (PFC)
  - Emotional lability, depression

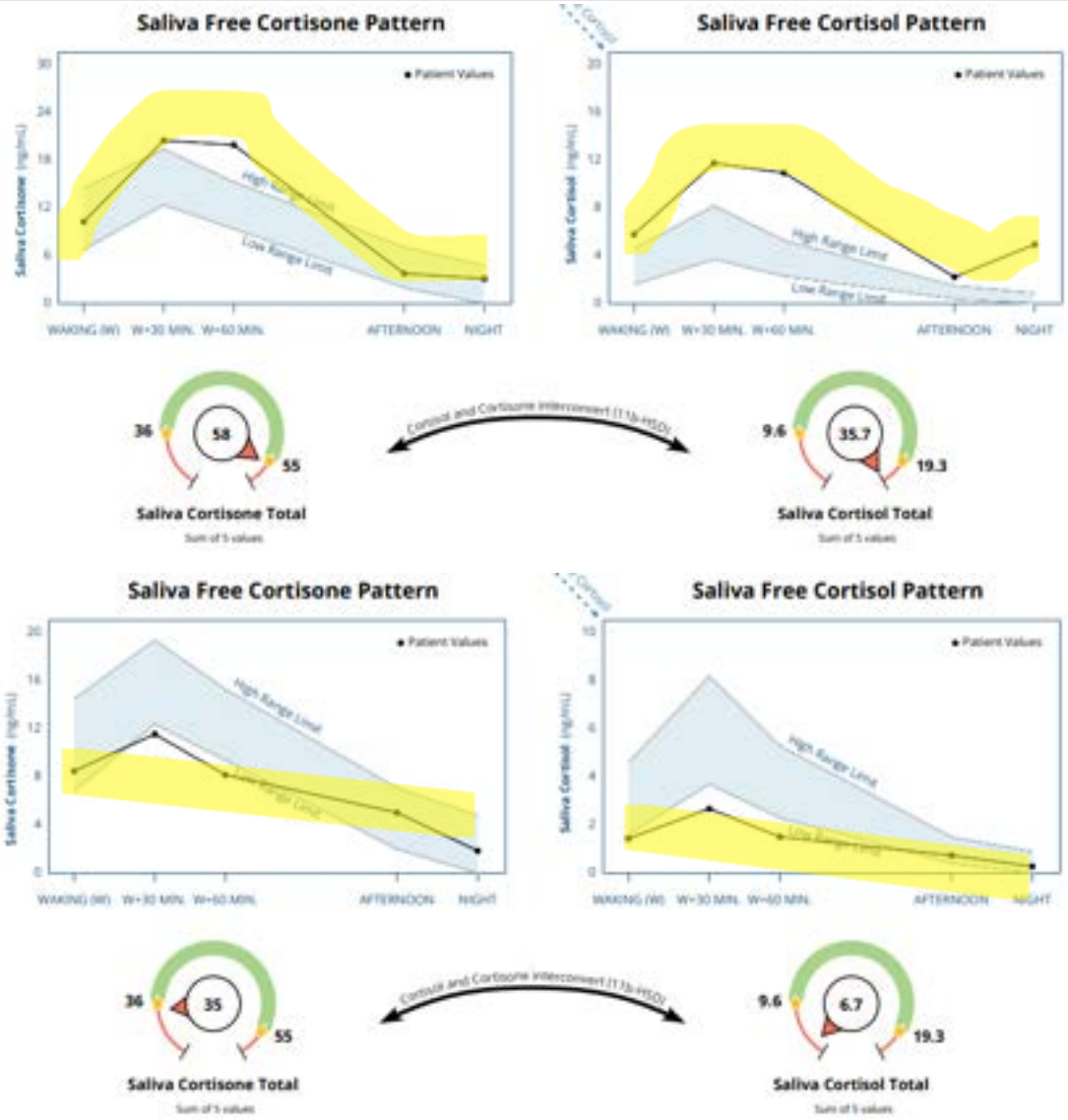
- Overall Low Cortisol
  - Irritability, apathy, depression





Assess Diurnal Pattern Shape

- Diurnal Free Cortisol Pattern shows ***highs at odd times*** (afternoon, night, high CAR) - Melancholic type

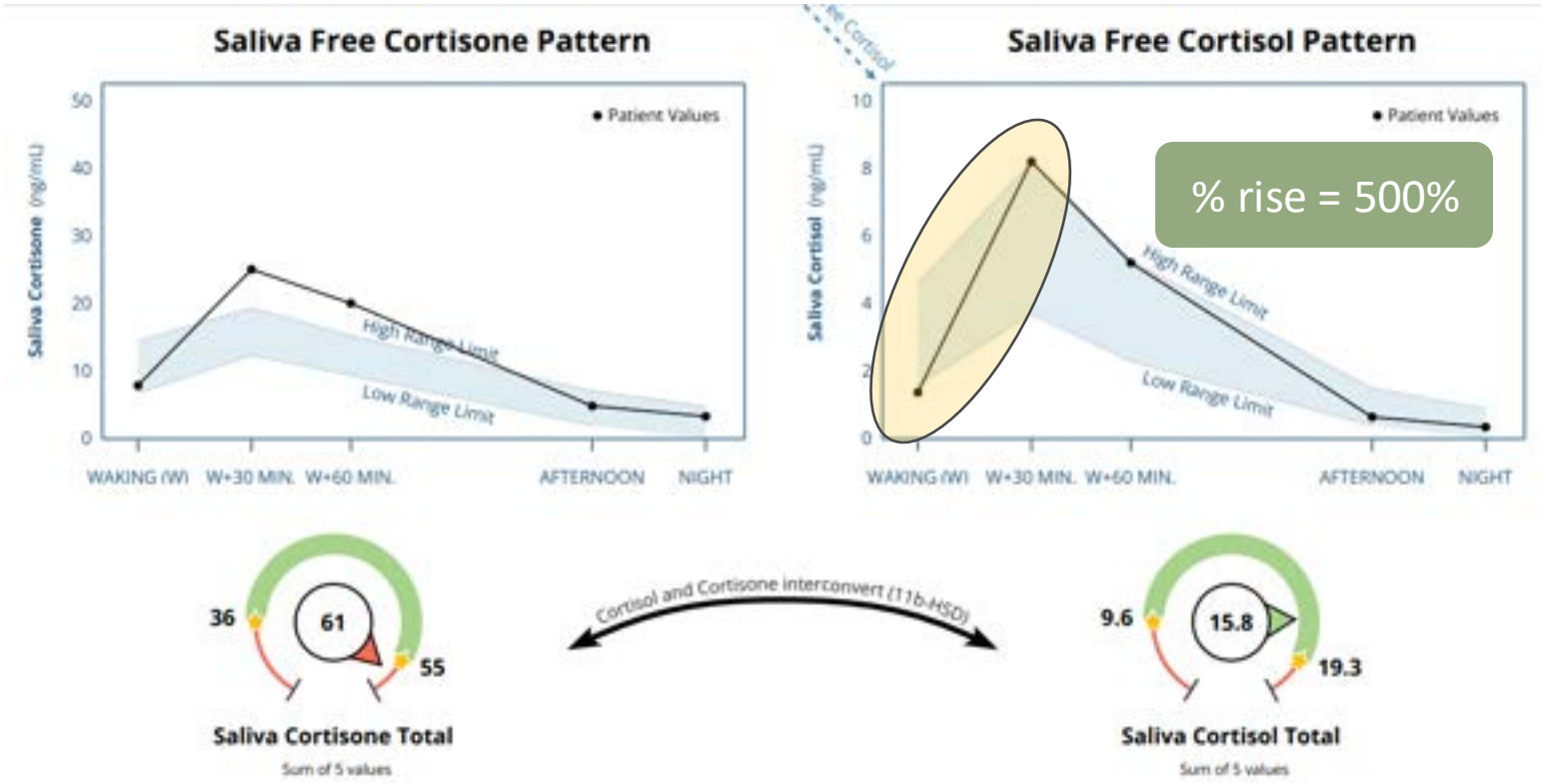


- Flattened slope diurnal pattern – Atypical type
  - Most common free cortisol pattern in chronic depression when coupled with a high cortisol clearance rate

Assess the Magnitude of the CAR (Stress Response to Waking)

- The Cortisol Awakening Response is often abnormal in depression – elevated

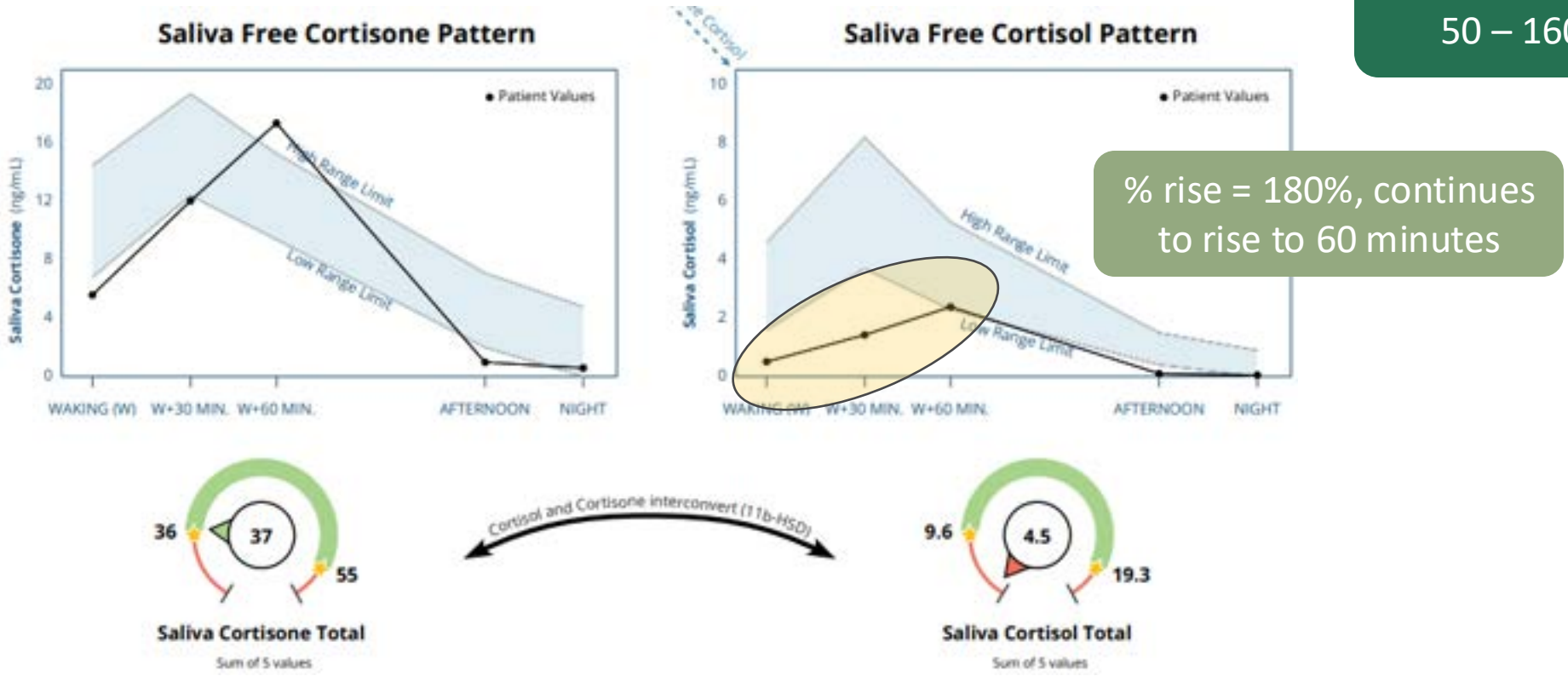
% rise shoud be
50 – 160%



Assess the Magnitude of the CAR (Stress Response to Waking)

- The Cortisol Awakening Response is often abnormal in depression - prolonged

% rise shoud be 50 – 160%



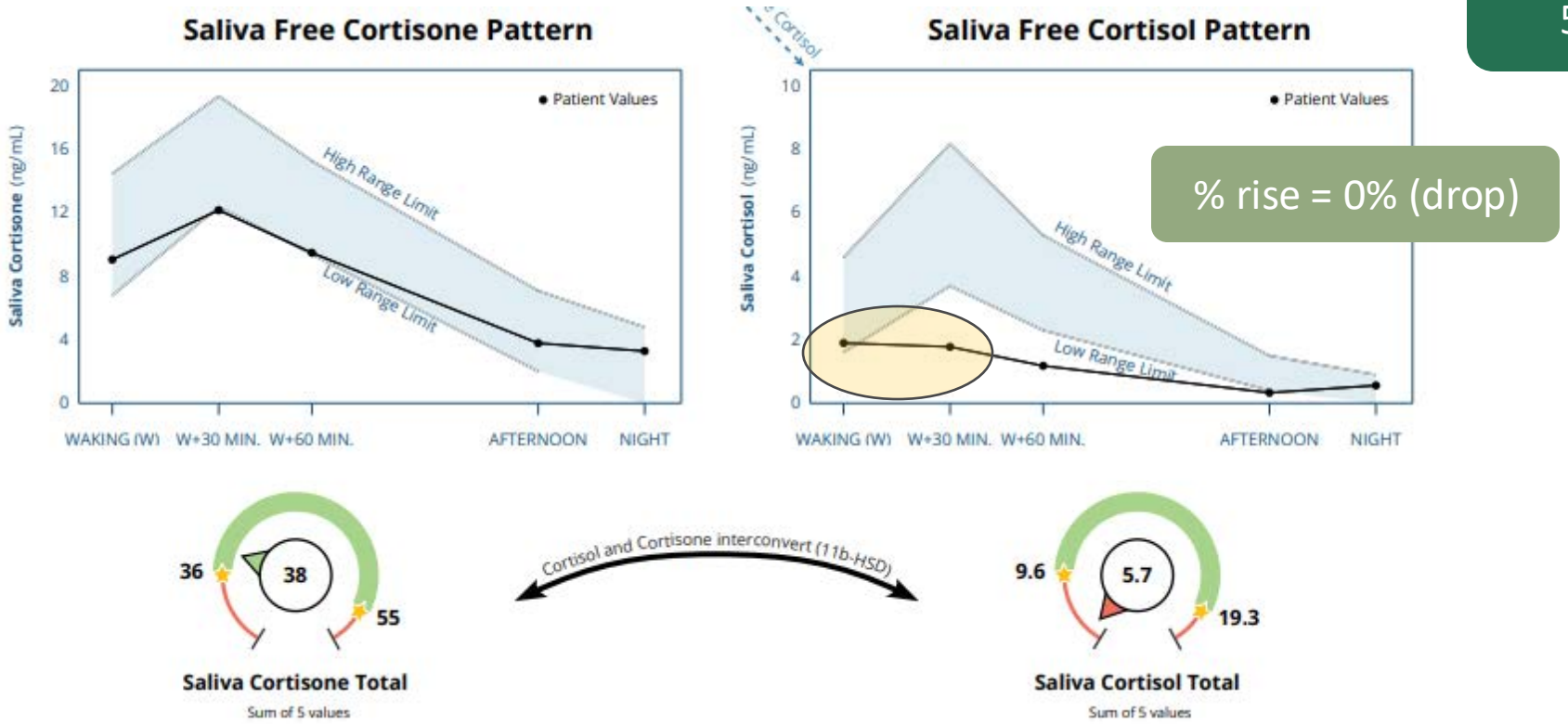
High and Prolonged CAR

- A hallmark of mild to moderate and acute depression
- Magnitude of the HPA axis activation/cortisol production is higher than the need entails
- When the CAR is high, cortisol increases PNMT activation of NE --> Epi which can contribute to anxiety in some
  - Especially when COMT is low
    - COMT "clears" Epi --> inactive VMA

Assess the Magnitude of the CAR (Stress Response to Waking)

- The Cortisol Awakening Response is often abnormal in depression - low

% rise shoud be 50 – 160%

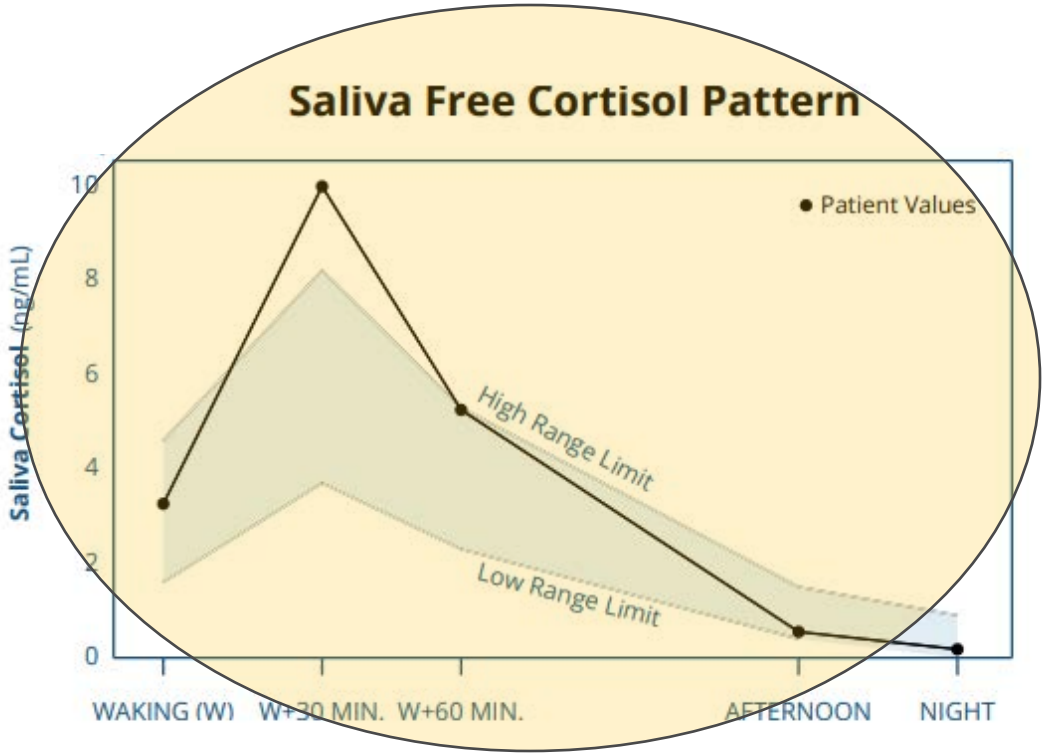


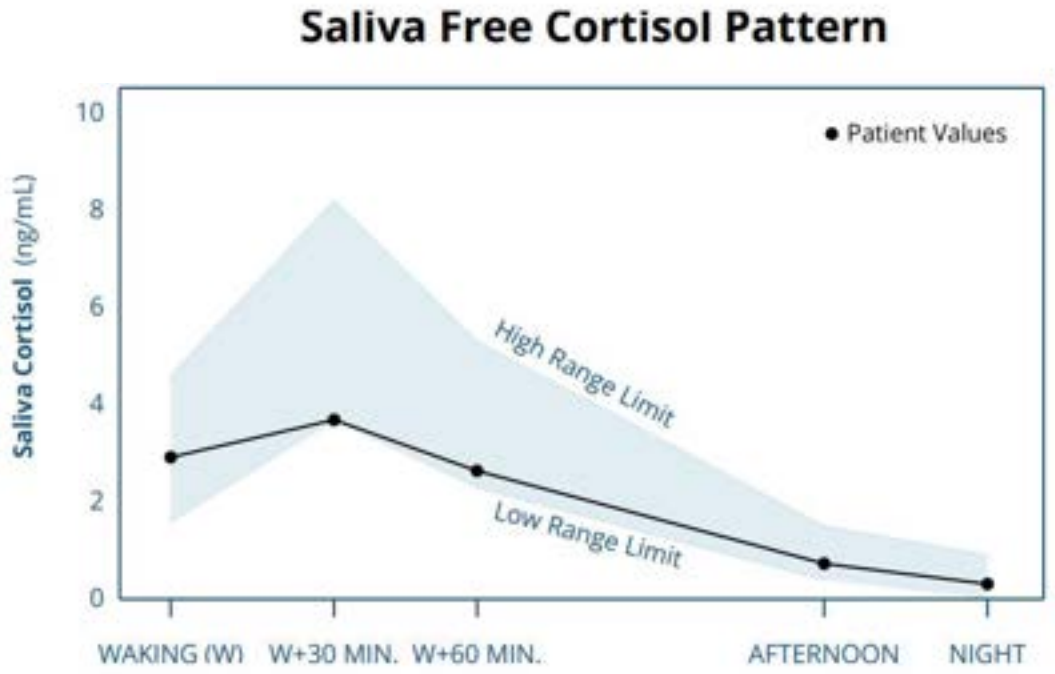
Low and Absent CAR

- A hallmark of severe or chronic depression
- When the CAR is low, the stress response is mostly managed by the CNS (NE and Epi). Feels like “running on pure adrenaline.”
- The blunting of the CAR results from a significant period of chronic stress/previously high cortisol.
- The blunted CAR represents cortisol’s long-term impact on HPA axis function and hippocampal volume loss.
- Treatment of a low CAR incorporates hippocampal supportive adaptogens that increase BDNF.

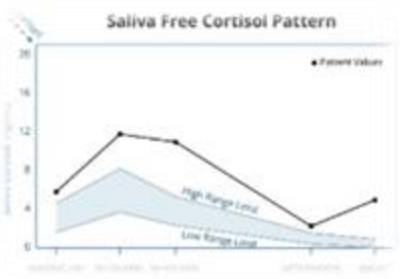
Do we treat these 2 patients' cortisol patterns in the same way?

- For which pattern would an SSRI work best?



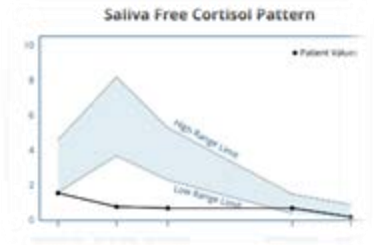


High Cortisol Types - Inhibitory and Parasympathetic Nervous System Supports



- Sleep Hygiene Practices and Regular Aerobic Exercise 3-4x weekly (walking, yoga, swimming)
- Stress Modulating Practices
  - Journaling, Meditation, Breathing, Mindfulness, HRV-Biofeedback, Emotional Freedom Technique, Music Therapy, Forest Therapy, Dance, Being Outside, Gargling, Havening…
- Probiotics
  - Bifidobacterium spp. and Lactobacillus spp.
- Melatonin and Serotoninergic Supports (if using serotonin supports with SSRI or SNRI, exercise cautious approach)
  - Melatonin, 5-HTP, MTHF, B6, B12, Curcumin, Rhodiola, Saffron, Tryptophan, Vitamin D
  - Estradiol replacement (if indicated) increases serotonin production in brain (TrpH-2) and SERT exp, dec MAO-A/B
  - Testosterone replacement (if indicated) increases SERT expression and binding
- GABAergic Supports
  - Oral GABA, B6, Glycine, Magnesium, Taurine
  - Allopregnanolone-forming: Progesterone therapy, Pregnenolone
- Herbal Adaptogens (modulate cortisol rhythm) and:
  - Promote GABA system: Ashwagandha, Bacopa, Holy Basil, Jujube, L-Theanine, Lemon Balm, Magnolia, Skullcap
  - Protect/Repair Hippocampus: Bacopa, Curcumin, Eleuthrococcus, Ginkgo biloba, Lion's Mane, Reishi, Rhodiola, Schisandra
- Nutritional Supports for Stress System
  - Choline (PC, CDP-choline, lecithin, αGPC), DHA (docosahexaenoic acid), EPA (eicosapentaenoic acid), Magnesium, Pantothenic Acid (B5), Phosphatidylserine, Specialized Pro Resolving Mediators, Vitamin C, D, Zinc….

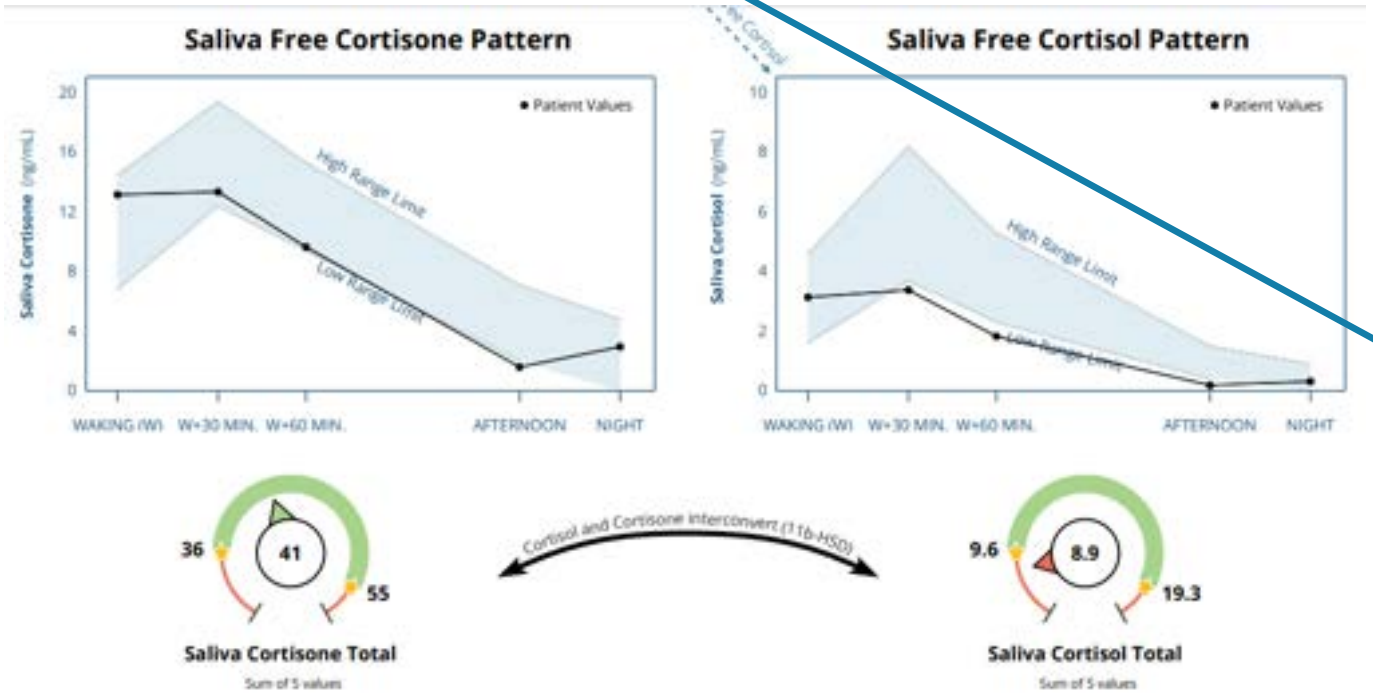
Low Cortisol Types – Restore HPA, Temper SNS

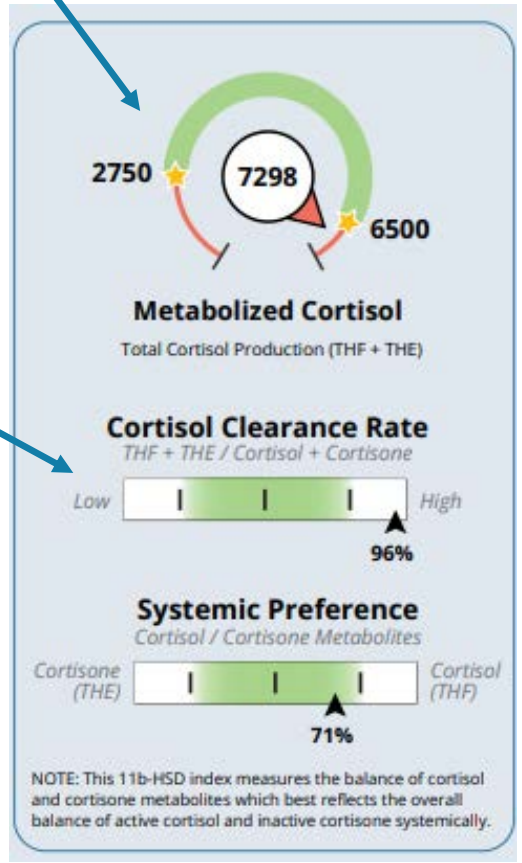


- Treat chronic, underlying conditions
- Consider influence of concurrent medications known to lower HPA axis activity:
  - Examples: Recent Corticosteroids (4-6 wks), Cannabis use, Opiates, SSRIs
- Combined Resistance and Aerobic Exercise
- Restore Mitochondrial Function/Activity
  - ALA, Antioxidants, Carnitine, CoQ10, NADH, Pregnenolone, Taurine
  - Sex hormone and/or androgen replacement including DHEA, if appropriate
- Nutritional Supports
  - B6, B9, B12, C, EFAs, Magnesium, Glandular adrenal tissue
- Increase Half life of Cortisol
  - DIM, Licorice Extract
- Gently Stimulate GRs w/ Energizing Adaptogens
  - Cordyceps, Epimedium, Ginsengs, Maca, Rhodiola, Shatavari
- Calming Herbs (Nervines)
  - Catnip, Chamomile, Hops, Kava, Lavender, Passion Flower, Valerian
- Reconnect Brain-Body
  - Vibration, Biofeedback/HRV training, Meditation, Breathing, Gargling, Sleep Hygiene practices

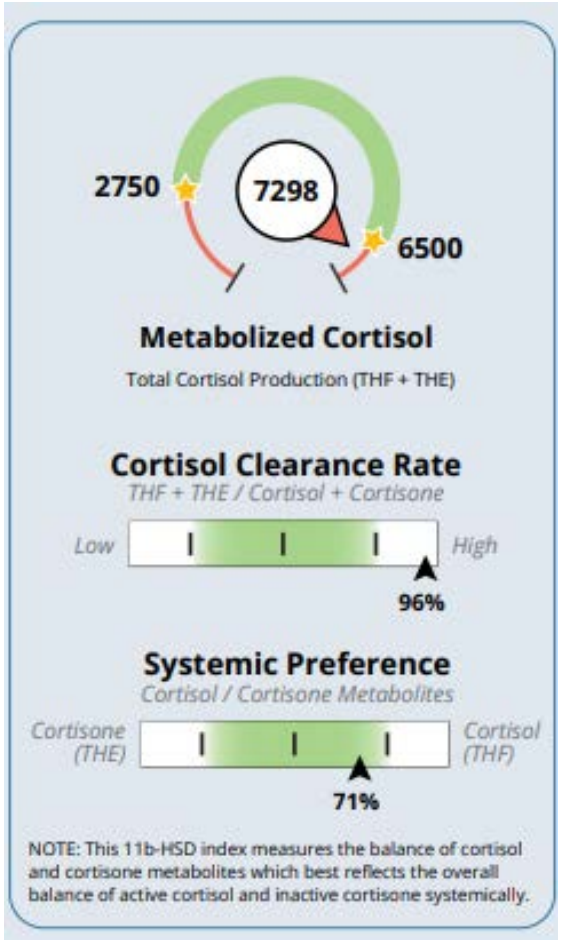
Don't Miss THIS Sign of High Cortisol on a DUTCH Plus Test

- The **Cortisol Clearance Rate** is high and the **Total Cortisol Metabolites** are elevated





High CCR Causes

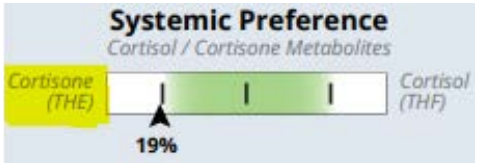


Top Considerations:

- Inflammation
- Insulin Resistance
- Infection
- Obesity
- Fatty Liver
- Elevated Leptin
- Sleep Apnea
- Hyperthyroid

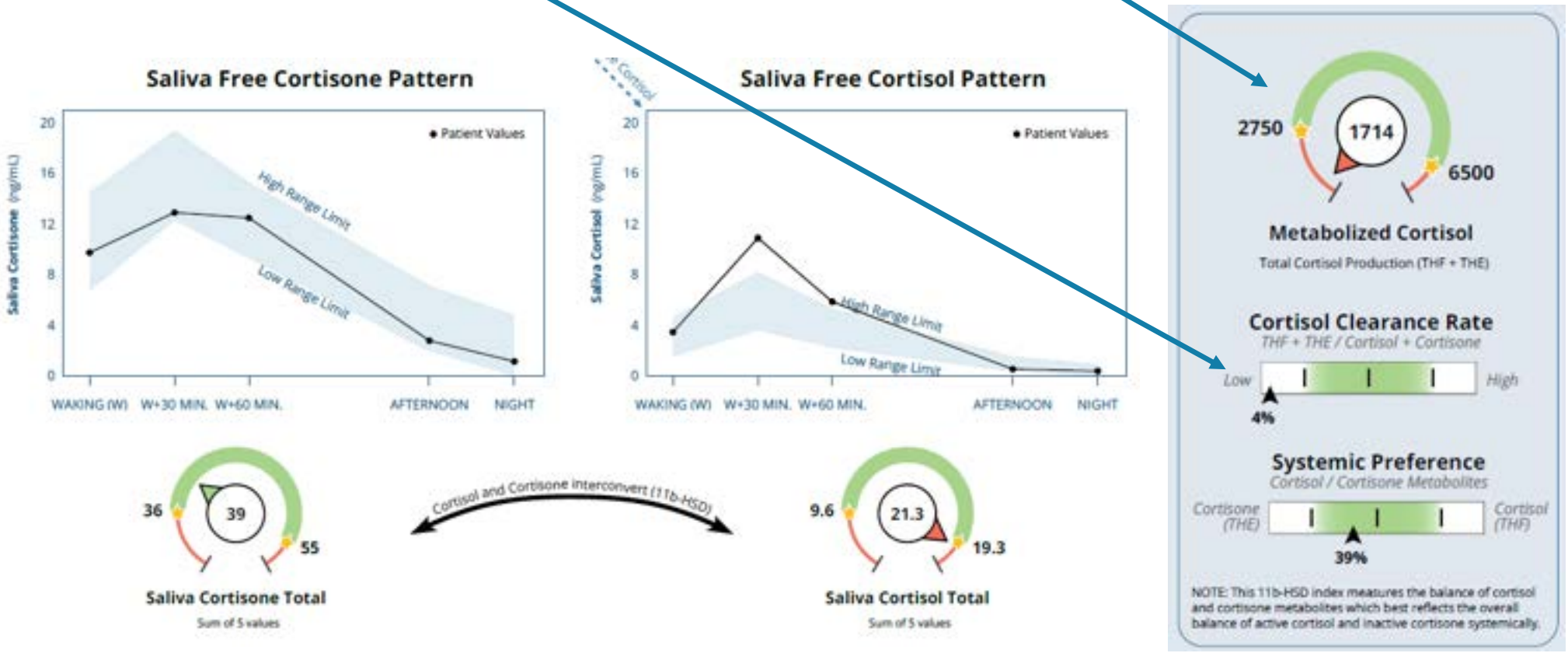
High CCR Treatment Goals in Depression

- Address inflammation/oxidative stress
  - AIP, Curcumin, EGCG, Enzymes (systemic), Exercise, Ginger, Medicinal mushrooms, Melatonin, Omega 3 (SPMs), Quercetin, Scutellaria
- Increase insulin sensitivity
  - ALA, Berberine, Bitter melon, Cinnamon, Chamomile, Mediterranean diet, Myoinositol…
- Modulate immune activity
  - Andrographis, Astragalus, Berberine, Cordyceps, Ginger, Plant sterols, Reishi, Scutellaria baicalensis, Sulforaphane…
- Assess for dysbiosis and treat gut
  - High OATs (Indican, B-hydroxyisovalerate), low Akkermansia mucinophila, Firmicutes/Bacteroidetes ratio, etc
- Rule out hyperthyroid
  - Adjust thyroid overprescription, etc
- Assess for metabolic dysfunction (leptin resistant, chronic cortisone dominant)
  - Especially if weight management is part of tx plan → PreDM, T2DM
  - 11BHSD1 inhibiting supports: Bitter Melon, Cinnamon, Curcumin, EGCG, Gymnema, Tangeretin

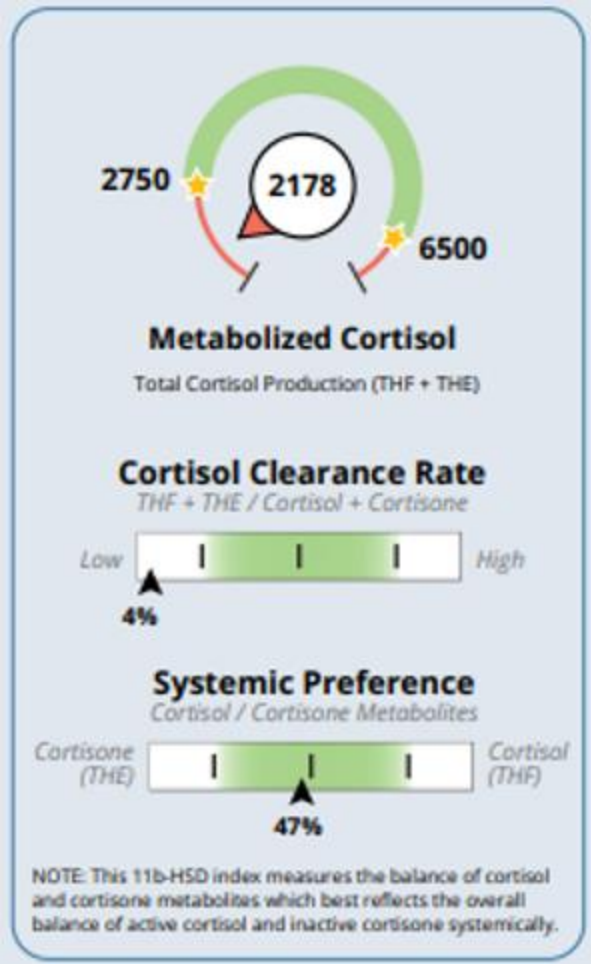


Free Cortisol Can Be High While Total Production is Low

- The **Cortisol Clearance Rate** is low and the **Total Cortisol Metabolites** are low



Low CCR Causes



Top Considerations:

- Hypothyroid (even subclinical)
- Anemia (iron deficiency)
- Mitochondrial dysfunction
- Liver/Gallbladder Stasis
- Low Caloric intake
- HPA Axis Dysfunction
- Medications (opiates, steroids...)

Low CCR Treatment Goals in Depression

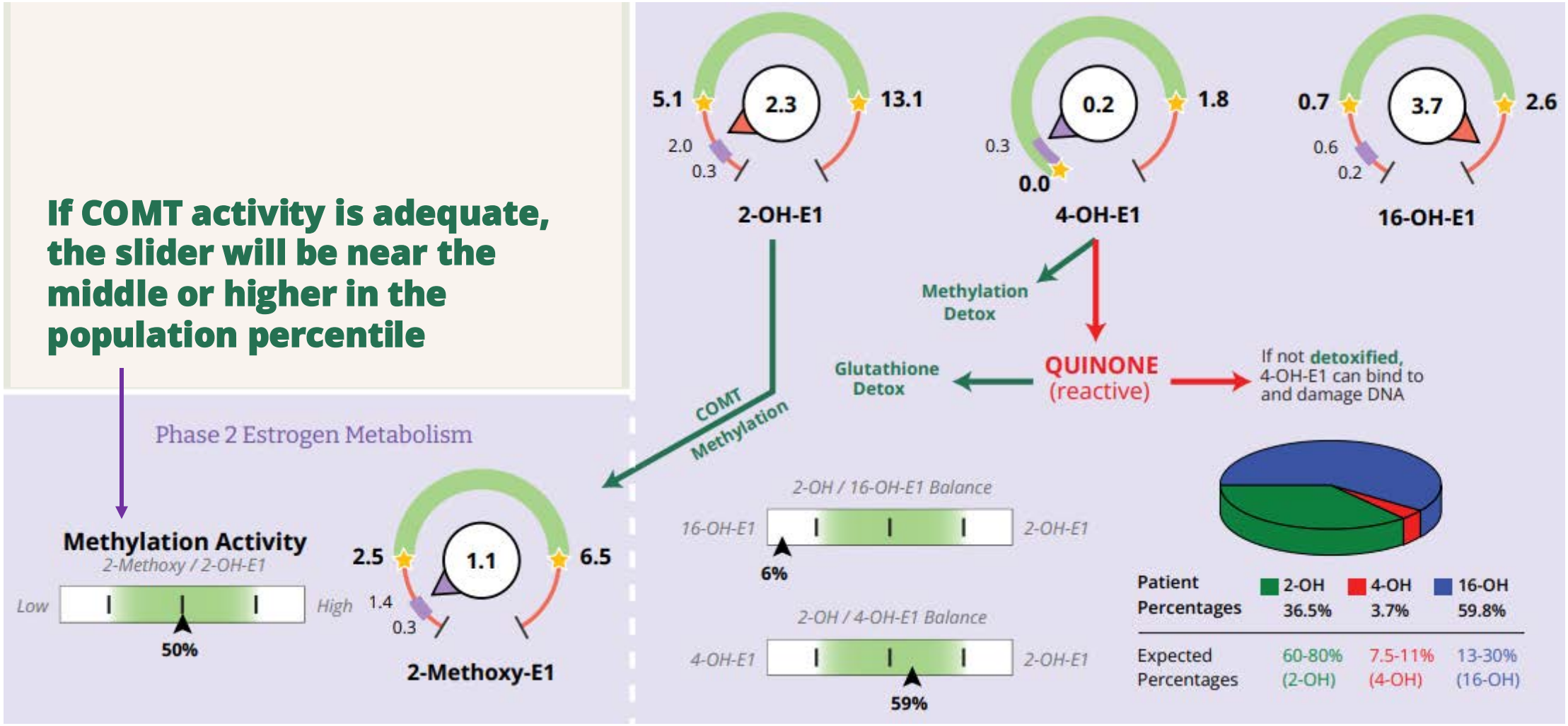
- Improve thyroid hormone levels if hypo on serum testing
  - Thyroid hormone replacement
    - T3 therapy may improve response to some antidepressant therapies (TCAs esp)
    - Iodine therapy if low dietary intake
  - T4→T3 conversion supports
    - Vitamins A, C, E, Sel, Zinc, B vits
- Improve gall bladder/liver function
  - Bile acids, Ox bile, lipotropic supports
- Increase mitochondrial function
  - CoQ10, ALA, Carnitine, Antioxidants, NADH, Taurine
  - If there's toxicity, detox and rebuild
  - Regular exercise (from yoga → HIIT, trial and individualize, reverse dieting)
- Expand caloric intake if inadequate or too low for physical activity level
  - Targeted nutrition
    - Treat underlying anemia by building the blood nutritionally (Fe, B6, etc),
    - Utilize adrenal and liver glandular formulas
    - Other generally trophic supports: B complex, C, EFAs, Multi-mineral formulas

COMT Enzyme Influences Moods

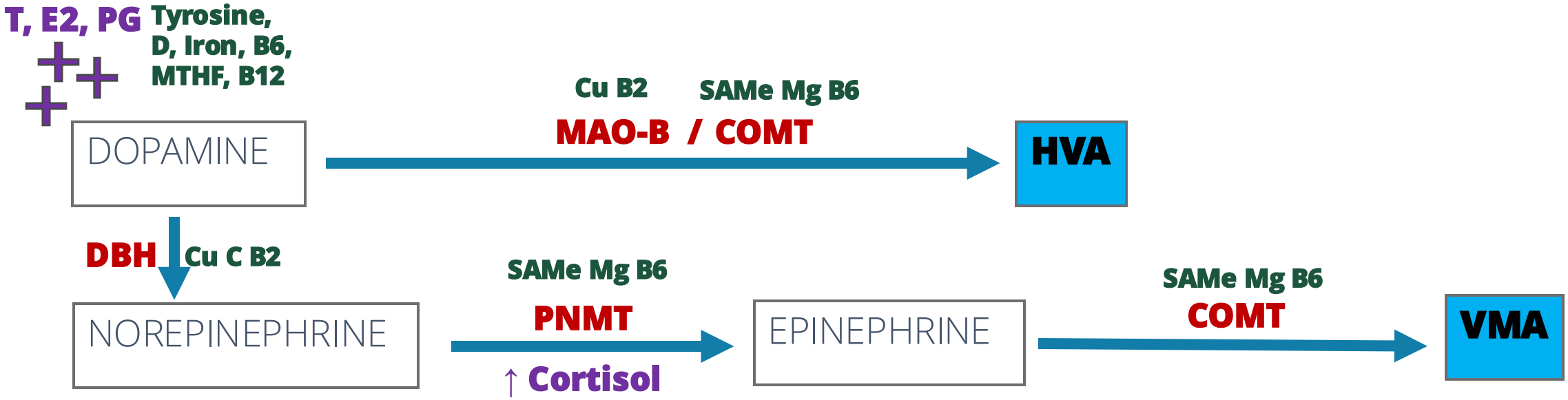
COMT/methylation Activity Level

- COMT methylates/inactivates estrogens
  - 2-OH-Es and 4-OH-Es → 2-MeO-Es and 4-MeO-Es
- COMT methylates/inactivates excitatory neurotransmitters
  - DA and NE/EPI → HVA and VMA
- High COMT dissipates/turns off activity of precursors
- Low COMT concentrates/perpetuates activity of precursors

DUTCH Assesses COMT Activity in the Context of Estrogen Metabolism



DUTCH Also Assess Neurotransmitter Post-COMT End Products, HVA and VMA



If HVA and/or VMA are LOW, before assuming low sympathetic tone, always go back and assess:

- COMT activity on PAGE 3
- Cortisol Production on PAGE 5
- B6 availability on PAGE 6 – Xanthurenate and Kynurenate

Treat lows here FIRST

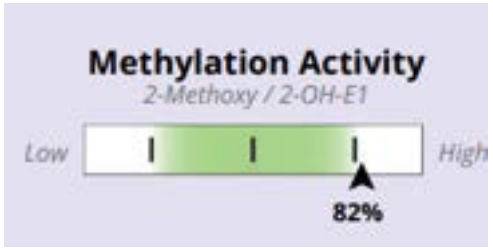
Vitamin B6 Markers - May be deficient if high		
Xanthurenate	Above range	3.30
Kynurenate	Above range	11.6

Both High and Low COMT Activity Can Impact Depression

COMT Fast

- Clears estrogens fast (low estrogen symptoms)
  - Bone loss, hot flashes, migraines, night sweats, sleep problems esp difficulty staying asleep
- Clears Dopamine fast (normal or high HVA and low dopamine symptoms)
  - Addiction, cravings, focus problems (and ADHD), low motivation, mood swings, risk-taking, weight gain
- Clears Norepinephrine and Epinephrine fast (normal or high VMA and low adrenaline symptoms)
  - Cognitive issues/brain fog, depression, fatigue, over-exercisers and under-eaters, risk-takers
- Fast COMT can be genetically driven (Val/Val of GG)
- **Fast COMT is associated with partial or non-response to antidepressant therapies but may do well with stimulants**

COMT Fast – Low Excitatory NTs, Lower Cortisol Types



COMT inhibitors: EGCG, Flavonoids, Quercetin, Resveratrol, Rhodiola

Gentle COMT Modulators:
Mag, Zinc, B complex incl B3

2-OH-E1 and E2
4-OH-E1 and E2

Dopamine

Norepinephrine

COMT

COMT

COMT

2-MeO-E1 and E2
4-MeO-E1 and E2

HVA

VMA

COMT Fast – Treatment Goals

- Temper COMT Activity:
  - EGCG
  - Flavonoids
  - Niacin
  - Quercetin
  - Resveratrol
  - Rhodiola
- Support SNS (DA and NE):
  - Curcumin
  - Ginkgo biloba
  - L-theanine
  - Mucuna pruriens
  - Rhodiola
  - Schisandra
  - St. Johns wort

COMT Slow

- Clears estrogens slowly (high estrogen symptoms)
  - Breast tenderness, heavy menses, mood disturbances, etc
- Clears Dopamine slowly (low HVA and high dopamine symptoms)
  - Anxiety, high perceived stress, sleep problems
- Clears NE and EPI slowly (low VMA and high adrenaline symptoms)
  - Anxiety, high perceived stress, sleep problems esp latent sleep onset
- Slow COMT can be genetically driven (Met/Met aka AA or Val/Met aka GA)
  - **COMT slow types associated with high cortisol levels in depression**
  - **Tend to respond to antidepressants**

Walder DJ, et al. Psychiatr Genet. 2010;20(4):166-170.

COMT Slow – Excitatory Dominance in CNS, Increased Cortisol Types

B12, Choline, MTHF, Methionine, Zinc

SAMe, B6, Magnesium

2-OH-E1 and E2
4-OH-E1 and E2

Dopamine

Norepinephrine

COMT

COMT

COMT

2-MeO-E1 and E2
4-MeO-E1 and E2

HVA

VMA

COMT Slow – Treatment Goals:

- Support Methylation:
  - B complex (with methylated forms incl MTHF)
  - Choline
  - Creatine
  - Magnesium
  - SAMe (caution with bipolar due to case reports of SAMe triggering mania)
  - Sulforaphane
  - Trimethylglycine (TMG/Betaine)
- Support Inhibitory NTs:
  - GABA
    - B6, GABA, Glycine, Magnesium, Taurine, Valerian, Allopregnanolone-forming hormones (Progesterone, Pregnenolone), Adaptogenic botanicals: Ashwagandha, Bacopa, Jujube, Lemon Balm, Magnolia, Mimosa, Skullcap
  - Serotonin
    - 5-HTP (caution with SSRI), B6, B12, MTHF, Rhodiola, Saffron, Tryptophan, Vitamin D

Sex Hormones

BALANCE is crucial for regulating immune and inflammatory responses that affect the HPA axis and NTs

Estrogens

Estradiol = Critical Factor in Female Depression

Review

Role of estrogen in treatment of female depression

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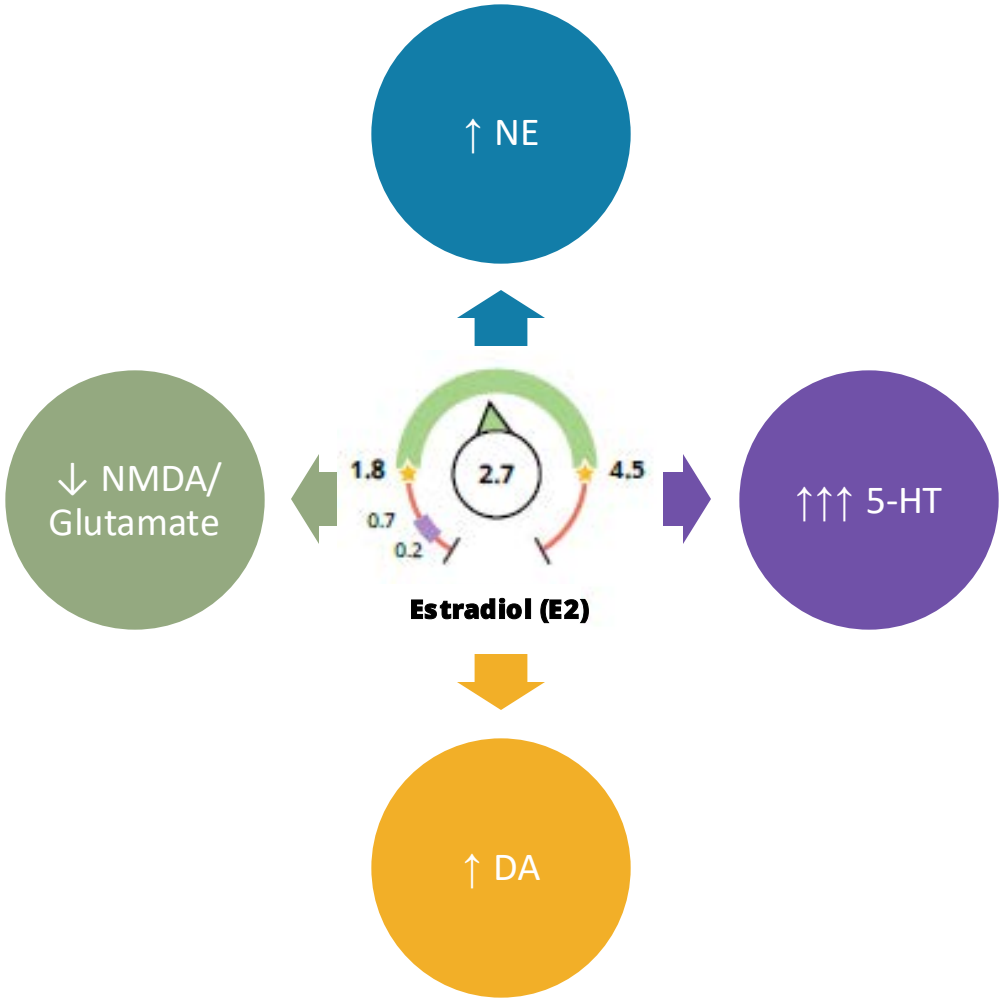
ABSTRACT

Depression is a neurological disorder that profoundly affects human physical and mental health, resulting in various changes in the central nervous system. Despite several prominent hypotheses, such as the monoaminergic theory, hypothalamic-pituitary-adrenal (HPA) axis theory, neuroinflammation, and neuroplasticity, the current understanding of depression's pathogenesis remains incomplete. Importantly, depression is a gender-dimorphic disorder, with women exhibiting higher incidence rates than men. Given estrogen's pivotal role in the menstrual cycle, it is reasonable to postulate that its fluctuating levels could contribute to the pathogenesis of depression. Estrogen acts by binding to a diversity of receptors, which are widely distributed in the central nervous system. An abundance of research has established that estrogen and its receptors play a crucial role in depression, spanning pathogenesis and treatment. In this comprehensive review, we provide an in-depth analysis of the fundamental role of estrogen and its receptors in depression, with a focus on neuroinflammation, neuroendocrinology, and neuroplasticity. Furthermore, we discuss potential mechanisms underlying the therapeutic effects of estrogen in the treatment of depression, which may pave the way for new antidepressant drug development and alternative treatment options.

- Estrogen changes over the course of a female's life
- Plays a critical role in mood regulation
- **Depressive symptoms tend to occur when E2 levels are low or take on a downward trajectory**

Estradiol Promotes NT Balance in Brain and is Particularly Pro-Serotonin



- Pro-Serotonin activities of Estradiol:
  - Increases transcription of Tryptophan Hydroxylase (brain type 2) enzyme = more 5-HT synthesis
  - Increases expression of 5-HT transporters to increase serotonin's message transmission
  - Inhibits MAO-A (decreases clearance of 5-HT, DA, and NE)
  - Decreases serotonin reuptake (natural SSRI)

Estradiol Modulates the HPA Axis – "an endogenous adaptogen"

- Estrogen receptors in the hypothalamus directly bind E2 to keep the stress response "normal"
  - ERa = up-regulating
  - ERb = down-regulating
- E2 also stimulates BDNF in the hippocampus to further modulate HPA axis/stress response
- Estradiol levels too HIGH (chronically) can increase HPA axis reactivity to stress (too much ERa) → depression, anxiety, etc.
- Estradiol too LOW can increase HPA axis reactivity to stress (too little ERb) → depression, anxiety, etc.

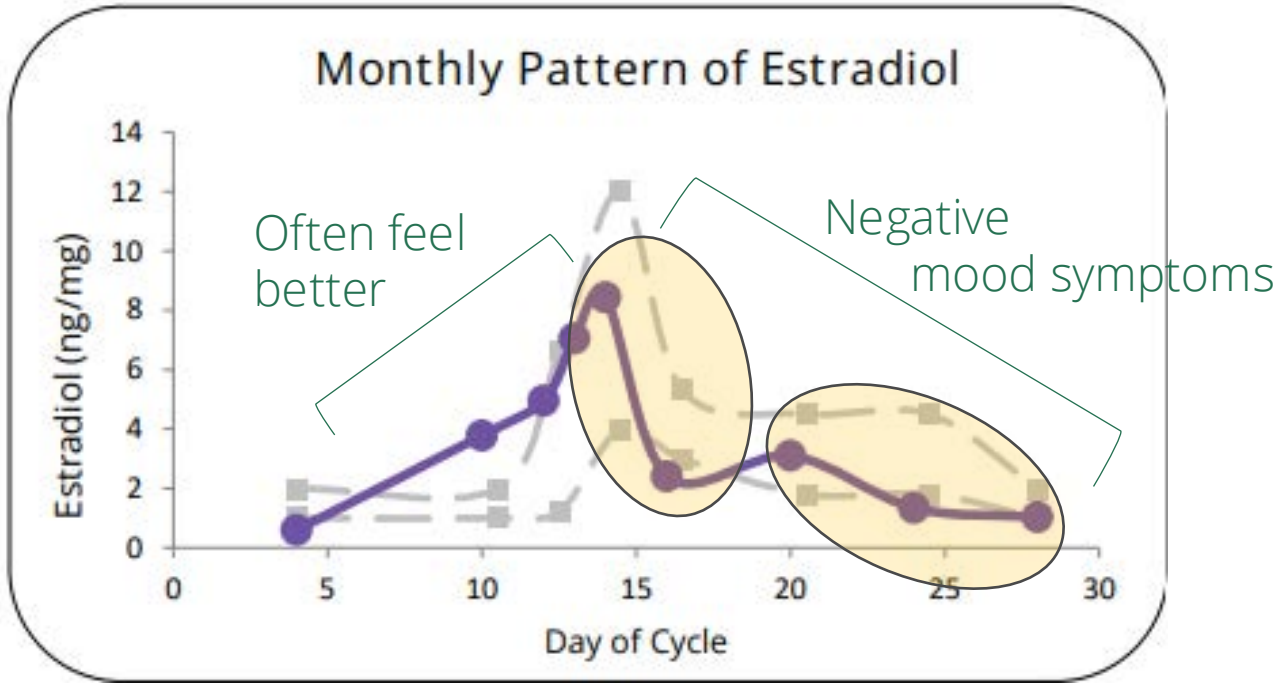
Estradiol Drops and Lows Promote Faster Clearance of 5-HT and NE

- Result is depression, mood swings that can be cyclic with characteristic drops in estrogen during the menstrual cycle (during ovulation and before menses), fatigue, anxiety, migraines, and cognitive issues.

E2 and Depression: Key Windows of Vulnerability

In Females: Mood Changes Occur When E2 Levels Decline

- During the menstrual cycle
  - Cyclic swings from higher to lower E2 levels with the menstrual cycle can trigger neurotransmitter imbalances that lead to mood dysregulation

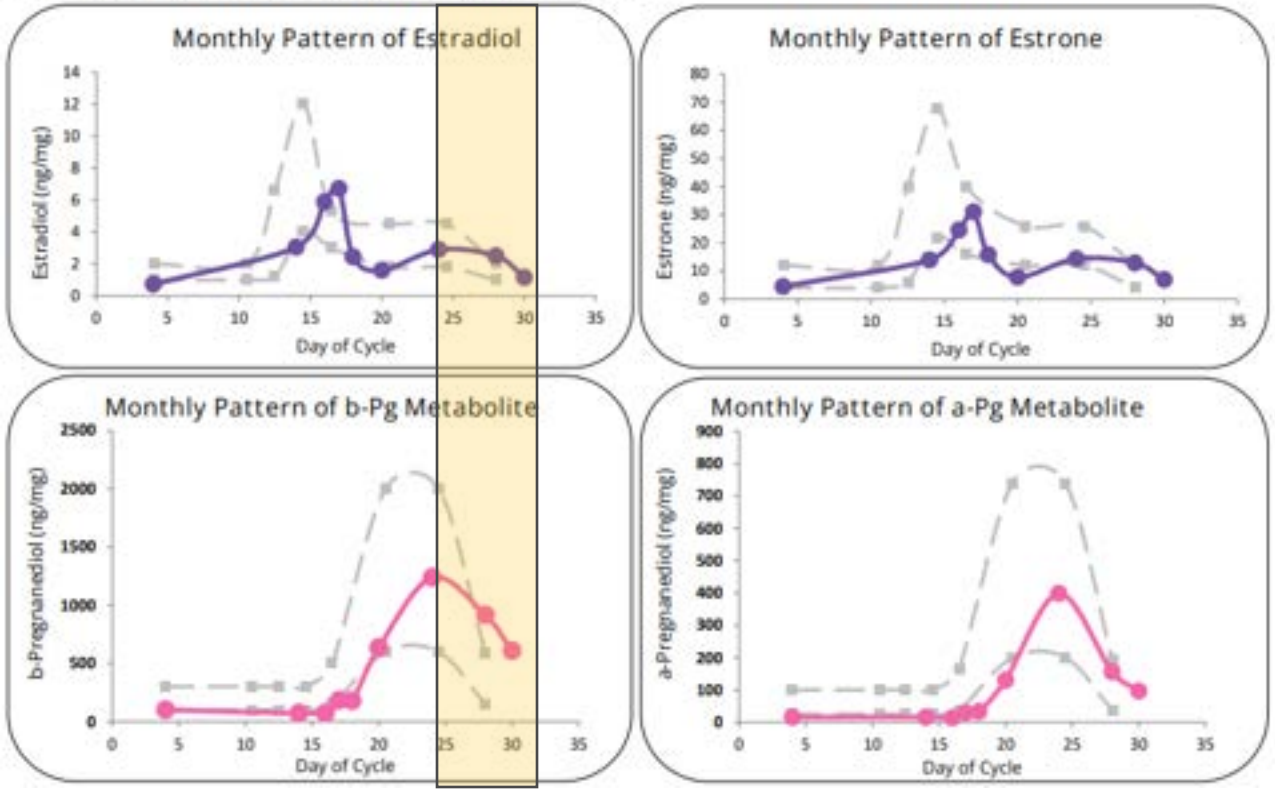


When progesterone also drops – GABA and Serotonin flux → Mood Instability

Common exacerbation time: Natural E2 and PG decline after mid-luteal plateau

Ex: PMS and PMDD

Estrogen (E) patterns can be seen below in purple. Progesterone (Pg) patterns can be seen below in pink. Normal ranges are within the gray dashed lines. See page 2 for more information.



In Females: Mood Changes Occur When E2 Levels Decline

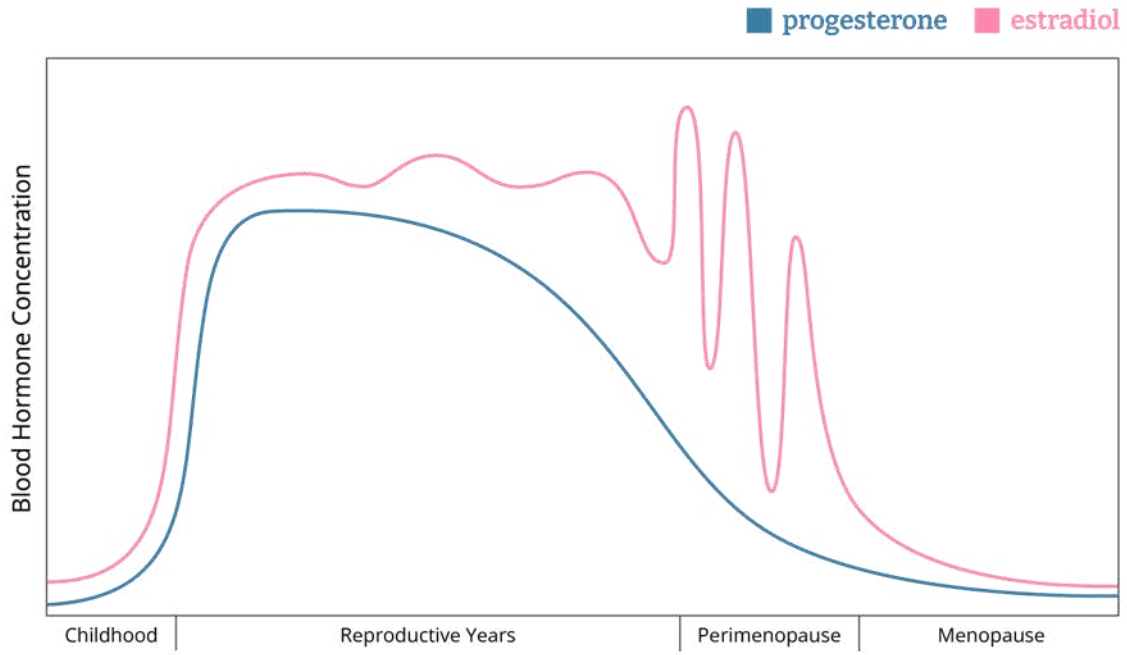
During postpartum

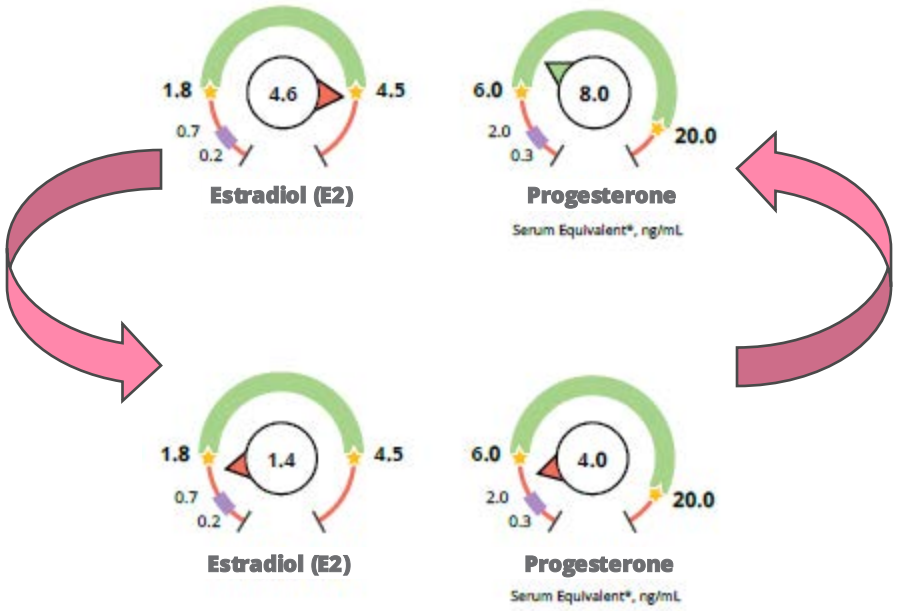
- The drop in E2 and progesterone after giving birth can trigger neurotransmitter imbalances that lead to mood dysregulation if neurochemistry is slow to “bounce back”

In Females: Mood Changes Occur When E2 Levels are Erratic

During perimenopause

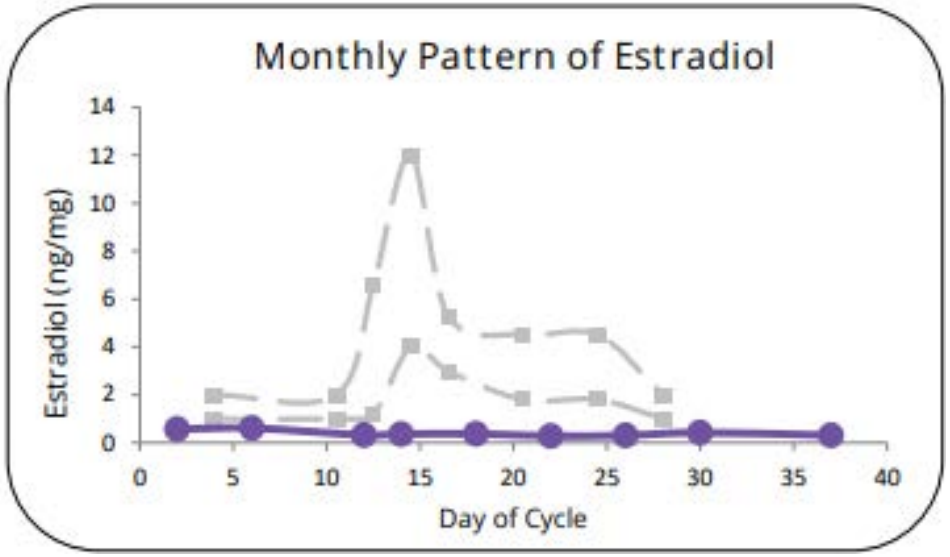
- The erratic nature of E2 in perimenopause triggers neurotransmitter imbalances that lead to mood dysregulation

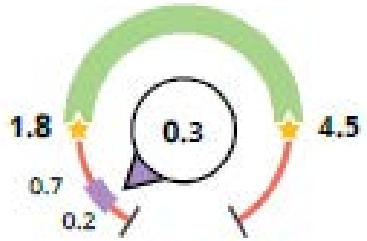


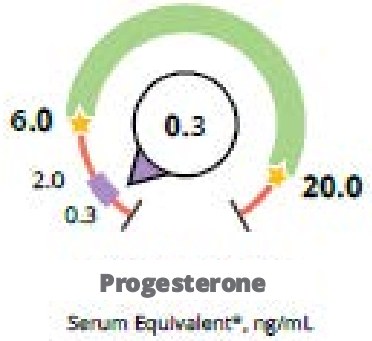


In Females: Mood Changes Occur When E2 Levels are Sustained Low

During menopause

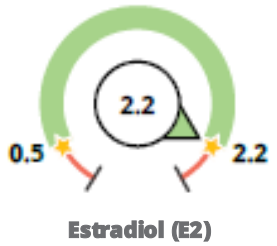


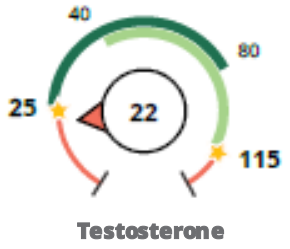




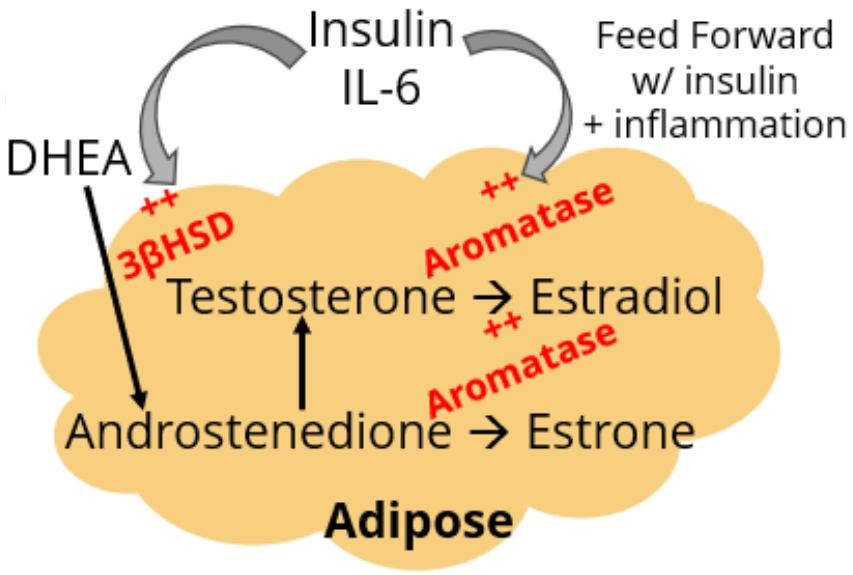
In Males: Mood Changes Occur When E2 Levels are Elevated (esp young men)

- High E2 is associated with depression in younger men regardless of BMI but may be exacerbated with adipose tissue dysfunction as men age.





- High Aromatase Activity --> Androgens are "lost" to estrogen production
  - Aromatase up-regulated in:
    - Stress
    - Inflammation
    - Insulin resistance
    - Metabolic Syndrome
    - Obesity



In Males: Mood Changes Occur When E2 is Low with Low Testosterone

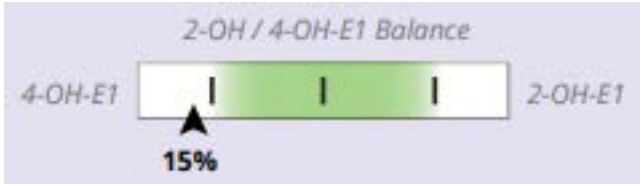
- Low E2 in males can affect side effect profile of some antidepressants.
- In older males, low pre-treatment estradiol may predict sexual side effects when SSRIs are used.

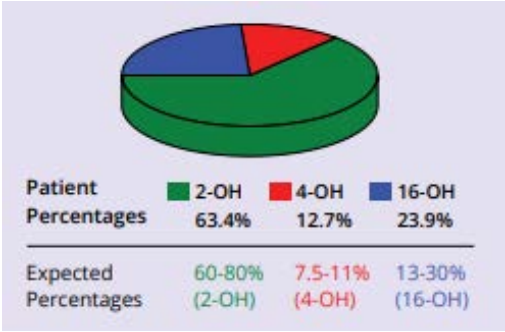
Jensen KHR, et al. Neuroscience Applied. 2024;3.

The Way Estrogen is Metabolized Can Provide Clues to Contributing Factors in Depression

Low 2-OH : 4-OH Ratio

- Inflammation
- Genetics – CYP1B1 snp
- Toxic Exposures
  - PAHs
- Mold Toxins
  - Aflatoxin B1
  - Zearalenone





When 2-OH : 4-OH ratio is low, check for other DUTCH signs of inflammation

Depression is rooted in chronic inflammation

- Elevated:
  - 5a-Reductase Activity
  - Pyroglutamate
  - Quinolinate
  - Free cortisol and/or free cortisone
  - Total Cortisol Metabolites (TCMs)

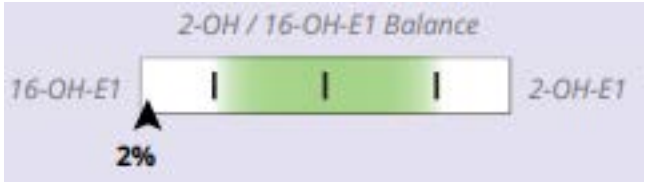
- Associated lows:
  - DHEA-s
  - 6-OH-Melatonin-s

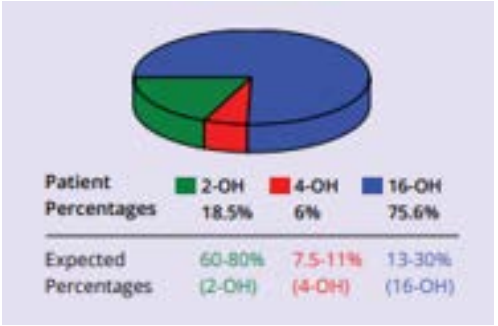
Treatment Options for 4-OHE Dominance – Low 2-OH : 4-OH Ratio

- Treat underlying inflammation if present.
  - Key nutraceuticals: Bromelain, Curcumin, EGCG, Ginger, Quercetin, Sulforaphane
  - Key anti-inflammatory hormonal supports: Melatonin, Vitamin D
  - Find the source if possible and treat there – toxic exposures, gut issues, immune, etc
- Use Antioxidants esp if 8-OHdG is also high.
  - Foods:
    - Brassicas, Citrus fruit, Red pepper, Tarragon, Rosemary
  - Flavonoids and Polyphenols decrease CYP1B1 expression:
    - Apigenin, Citrus bioflavonoids, Curcuminoids, EGCG, Hesperidin, Quercetin, Resveratrol, Rutin
- Test for and treat mold toxicities (or refer).

Low 2-OH : 16-OH ratio

- Caffeine
- Hyperthyroid
- Obesity
- Moderate Alcohol Consumption
- Pesticides exposures
- Smoking
- Medications and supplements can affect it (long list including St. Johns wort)
- High 16-OH-E1is associated with high prolactin levels, **gut dysbiosis**, autoimmune diseases (esp RA and SLE) and high DHEA





Note: 16-OH-E1 is the CYP3A4 metabolite of estrone which prefers ERa receptors and DOES bind estrogen receptors in the brain. High IL-6 in depressed patients increases 16-OH-E1 autoantibodies which contributes to chronic inflammation.

Treatment Options for 16-OH-E1 Dominance – Support Phase One

Lower 16-OHE1 levels:

- **Correct known drivers of high 16-OHE1.** (previous slide 66)
- **Trans-Resveratrol**
  - Net effect: decreased 16OHE1 and 4OHE1/4OHE2
  - May compete/inhibit estrogenic activity at tissues, often used with Quercetin
  - Common dosing: 100-500 mg daily
- **Rosemary Extract**
  - Net effect: decreased 16OHE1, increased 2OHE1/2OHE2
  - Often found in combinations with DIM or I3C, also anti-inflammatory
  - Follow bottle for dosing (can affect blood pressure in some people)

Shift toward 2-OHE1/2 pathway:

- 150-min moderate to vigorous aerobic **exercise** per week
- **DIM/I3C** (Diindolylmethane/Indole-3-Carbinol) – (hard core)
  - Therapeutic Dosing 100-300 mg daily
  - Some will d/c during menses and resume day 7
- **Sulforaphane** (gentle)
- **Ground flax**
- **Root veggies**: Spanish black radish, carrot, turnips, etc
- **Andrographis**
- **Omega-3s/SPMs**

Approaches to Low Estradiol-Influenced Depression

Menopausal:

- Estradiol therapy
- Progesterone therapy
- DHEA therapy (E1 precursor)
- Botanicals and phytoestrogens that modulate or mimic estradiol's neurotransmitter-promoting activity in the brain:
  - Cimicifuga racemosa (Black cohosh), Dong Quai, Flaxseed, Hops extract, Lepidium meyenii (Maca)

Cycling Females:

- ID and treat underlying cause – hypothalamic, hyperprolactinemia, low body fat %, etc.
- Follicular and Ovulatory supports
  - DHEA, phytoestrogens, Maca, Tribulus, Shatavari
- Luteal supports
  - Vitex, White Peony, MyoInositol, Progesterone therapy

- **Males:**
  - Testosterone therapy if E2 is low due to low T
  - Clomiphene/Enclomiphene therapy
    - Be aware that some report mood swings and depression with use.
  - DHEA therapy
  - SHBG affinity modulators if SHBG is high:
    - Boron, Nettle root
  - Estradiol therapy more rare but useful when:
    - bone loss is co-occurring
    - androgen-deprivation therapy is on board with cognitive side effects

Approaches to High Estradiol-Influenced Depression

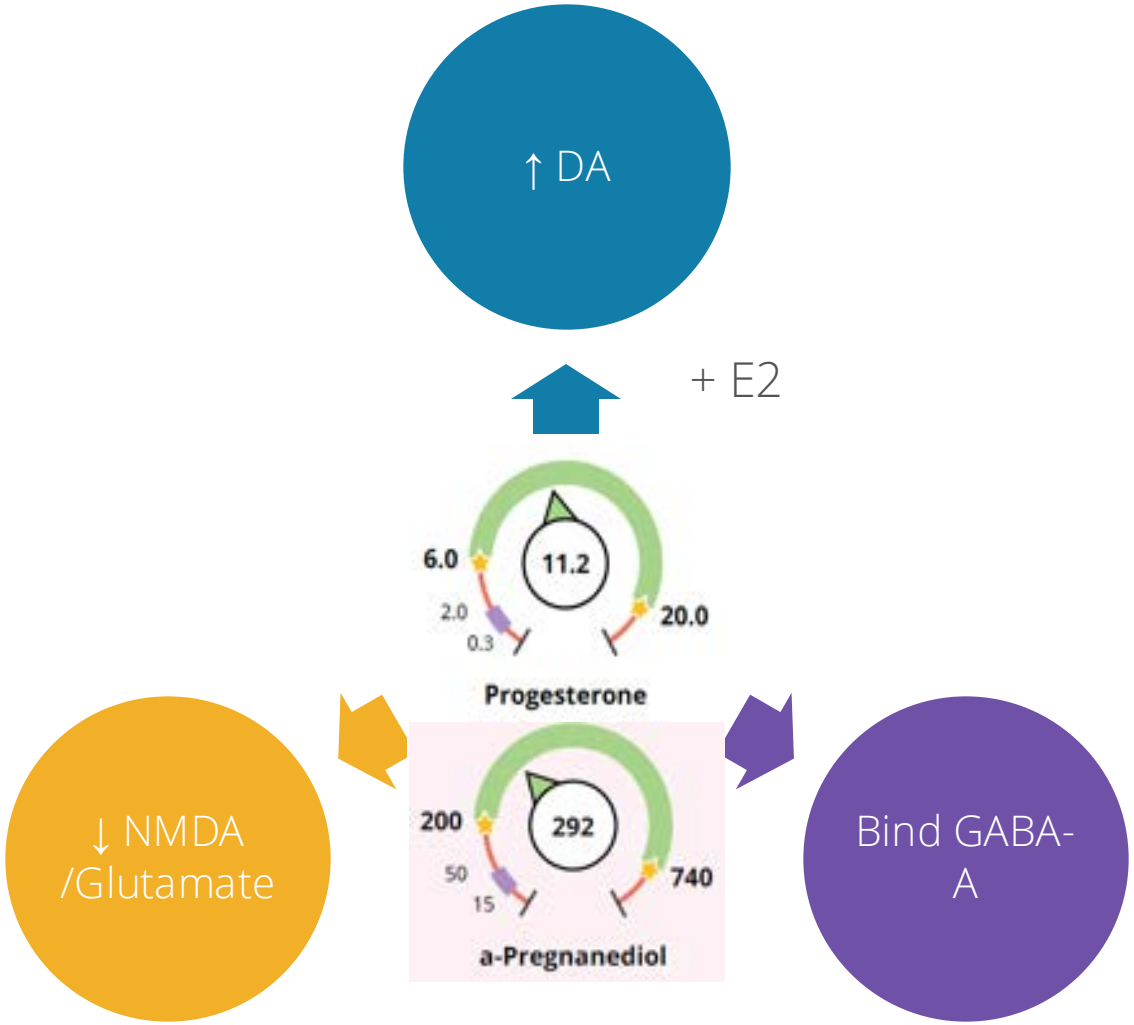
- **Females and Males**
  - Correct insulin resistance.
  - Encourage weight loss if appropriate.
  - Increase movement and exercise if sedentary.
  - Reduce inflammation.
  - Address GI microbial health, bowel transit, and digestion as indicated.
  - Calm HPA axis from E2 overstim if indicated.
    - Adaptogenic botanicals which are also phytoestrogens to bind ERb
      - Fo-Ti, Licorice, Maca
  - Support Estrogen Detox Phase 1 and 2
    - Citrus, Cruciferous and root veg, Flavonoids, Indole-3-carbinol, Resveratrol, Sulforaphane, etc
    - Methylation, sulfation, glucuronidation, and glutathione supports

Progesterone

Estradiol and Progesterone Work Synergistically in Females

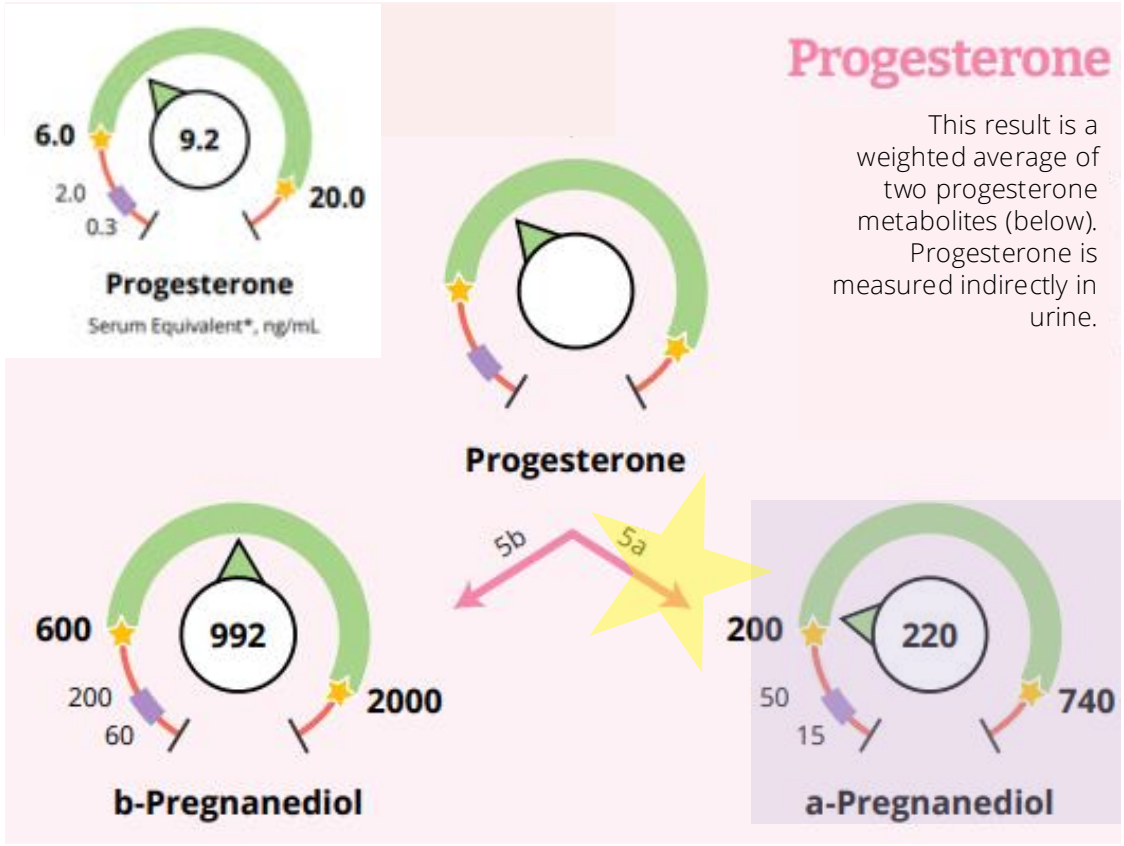
- Estradiol supports 5-HT, DA, and NE
- Progesterone metabolites bind GABA receptors and promote dopamine activity during luteal phase

Progesterone Affects Neurotransmitter Balance Too



- Progesterone Mood Mechanisms through a-pregnanediol/allopregnanolone:
  - Modulates estrogen rises and falls during the menstrual cycle (provides "padding" for highs, drops, and lows) by encouraging E2 → E1, sulfation of E1, and influencing E2 receptors
  - Binds GABA receptors
  - Down-regulates Glutamate Receptors
  - Modulates dopaminergic tone during luteal phase
  - Increases Lactobacillus spp. in the gut, improving mood from that angle

Progesterone in Females Affects Mood – Multiple Mechanisms



- Representation of Progesterone on a DUTCH test
- Progesterone is a serum equivalent calculation from b- and a-Pregnanediols
- A-pregnanediol informs us of this patient's GABA/Glutamate balancing potential
- A low level of a-Pregnanediol indicates low neurosteroid activity in the CNS from progesterone

Low Progesterone Indicated in Mood Disorders including PMDD

- Low progesterone/luteal insufficiency indicated in mood disorders and cyclic mood dysregulation (PMS, PMDD), sleep cycle dysregulation, anxiety
  - Extreme agitation during luteal phase when progesterone levels are naturally high or when patients use progesterone therapy within normal dosing ranges may indicate “paradoxical GABA response”
- Luteal Supports may be indicated:
  - Vitex, White Peony, MyoInositol, Progesterone therapy, etc.

A Cautionary Note about Progesterone and Negative Mood

- Some patients experience a “Paradoxical GABA Effect”
- Normal, physiologic luteal progesterone levels makes some people feel bad
- Inverse U dose-relationship in some patients with progesterone
  - Physiologic luteal levels = EXACERBATION
  - Follicular levels = FINE
  - Supraphysiologic levels = FINE
- Treatment options:
  - Suppress ovulation (GnRH agonists, combo OCPs)
  - Overrun GABA with supraphysiologic allopregnanolone (Andreen used 400 or 800mg USP progesterone suppositories)
  - Inhibit 5α–Reductase activity
    - Ganoderma (Reishi), Green tea (EGCG), Saw Palmetto, Nettle Root, Pygeum africanum
  - Myoinositol 600 mg – 2g daily

Andreen L, et al. Psychoneuroendocrinology. 2005;30(2):212-224.
Gianfranco C, et al. Hum Psychopharmacol. 2011;26(7):526-530.
Sundstrom-Poromaa I, et al. Front Neuroendocrinol. 2020;59.

Oral Micronized Progesterone

Reviews in Endocrine and Metabolic Disorders (2024) 25:751–772
https://doi.org/10.1007/s11154-024-09882-0

Diagnostic and therapeutic use of oral micronized progesterone in endocrinology

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Abstract

Progesterone is a natural steroid hormone, while progestins are synthetic molecules. In the female reproductive system, *progesterone* contributes to the control of *luteinizing hormone* and *follicle-stimulating hormone* secretion and their pulsatility, *via* its *receptors* on the *kisspeptin*, *neurokinin B*, and *dynorphin* neurons in the hypothalamus. *Progesterone* together with *estradiol* controls the cyclic changes of proliferation and decidualization of the endometrium; exerts anti-mitogenic actions on endometrial epithelial cells; regulates normal menstrual bleeding; contributes to fertilization and pregnancy maintenance; participates in the onset of labor. In addition, it exerts numerous effects on other endocrine systems. *Micronized progesterone* (*MP*) is *natural progesterone* with increased bioavailability, due to its pharmacotechnical micronized structure, which makes it an attractive diagnostic and therapeutic tool. This critical literature review aims to summarize and put forward the potential diagnostic and therapeutic uses of *MP* in the field of endocrinology. During reproductive life, *MP* is used for diagnostic purposes in the evaluation of primary or secondary amenorrhea as a *challenge test*. Moreover, it can be prescribed to women presenting with amenorrhea or oligomenorrhea for induction of withdrawal bleeding, in order to time blood-sampling for diagnostic purposes in early follicular phase. Therapeutically, *MP*, alone or combined with *estrogens*, is a useful tool in various endocrine disorders including primary amenorrhea, abnormal uterine bleeding due to disordered ovulation, luteal phase deficiency, premenstrual syndrome, polycystic ovary syndrome, secondary amenorrhea [functional hypothalamic amenorrhea, premature ovarian insufficiency], perimenopause and menopause. When administrated *per os*, acting as a *neurosteroid* directly or through its metabolites, it exerts beneficial effects on brain function such as alleviation of symptoms of anxiety and depression, aaw well as of sleep problems, while it improves working memory in peri- and menopausal women. *Micronized progesterone* preserves full potential of progesterone activity, without presenting many of the side-effects of *progestins*. Although it has been associated with more frequent drowsiness and dizziness, it can be well tolerated with nocturnal administration. Because of its better safety profile, especially with regard to metabolic ailments, breast cancer risk and veno-thromboembolism risk, *MP* is the preferred option for individuals with an increased risk of cardiovascular and metabolic diseases and of all-cause mortality.

Keywords Micronized progesterone · Amenorrhea · Oligomenorrhea · Menopause · Perimenopause · Hormone therapy

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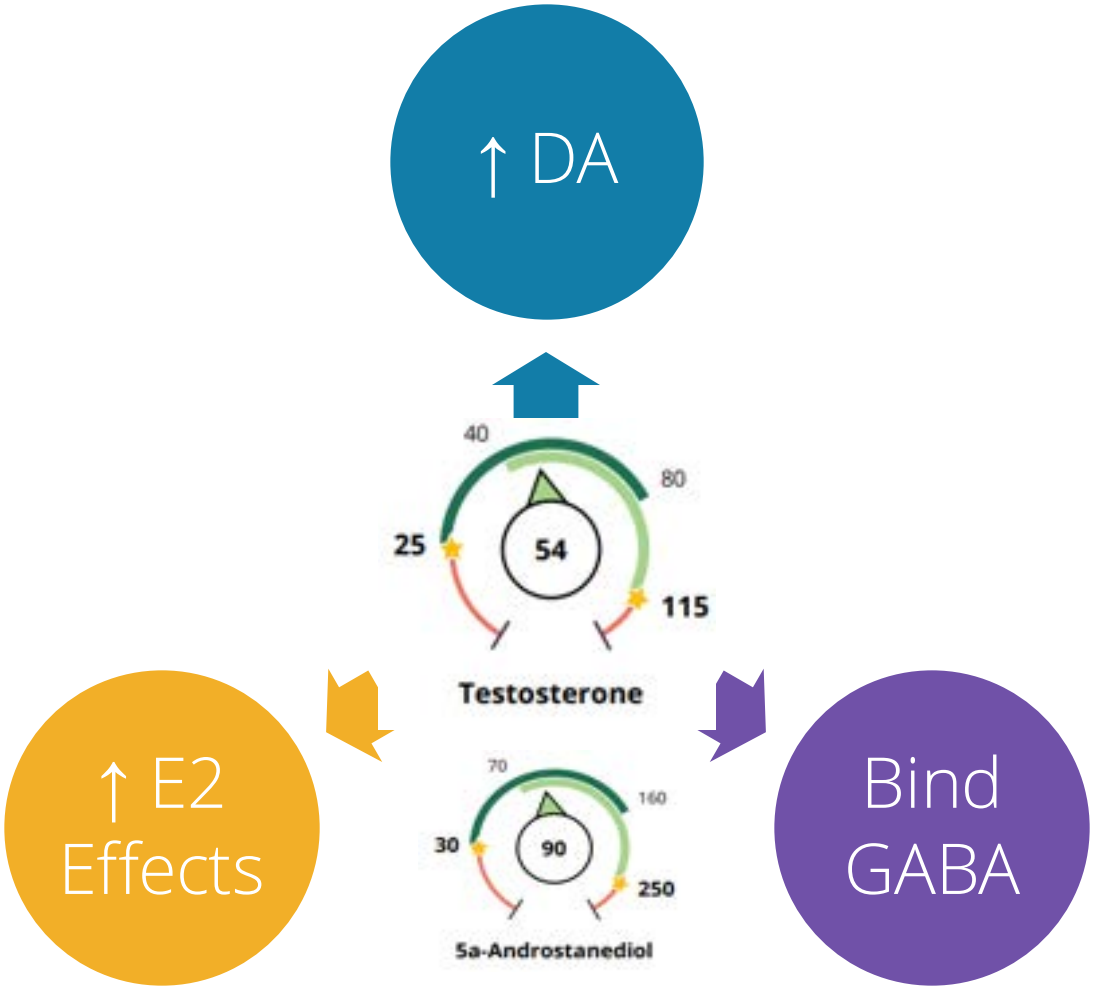
"When administrated per os, acting as a neurosteroid directly or through its metabolites, it exerts beneficial effects on brain function such as alleviation of symptoms of anxiety and depression, as well as of sleep problems, while it improves working memory in peri- and menopausal women."

Memi E, et al. Rev Endocr Metab Disord. 2024.

Androgens

Testosterone Affects Neurotransmitter Balance



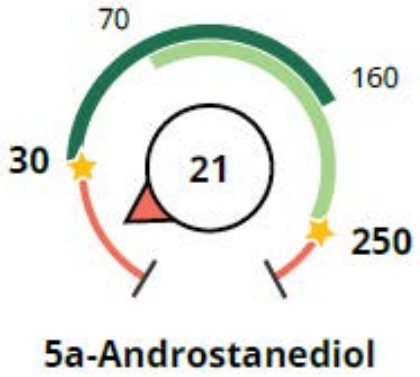
- Testosterone affects male and female neurochemistry differently
- Testosterone/5a-DHT increases dopamine activity in the brain
- 5a-Androstanediol = DHT marker in urine
- 5a-DHT converts to 5a,3a-Androstanediol which binds GABA receptors, anxiolytic at male levels
  - 5aR inhibitors like finasteride are associated with increased depression
- Testosterone converts to E2 via aromatase and then….
  - E2 supports DA, increases 5-HT, and NE

Low Testosterone Levels in Males Indicated in Depression

Abnormal Testosterone (DHT/5a-Androstanediol) in males

- High testosterone (esp high T/Cortisol ratio):
  - Agitation, anger, irritability

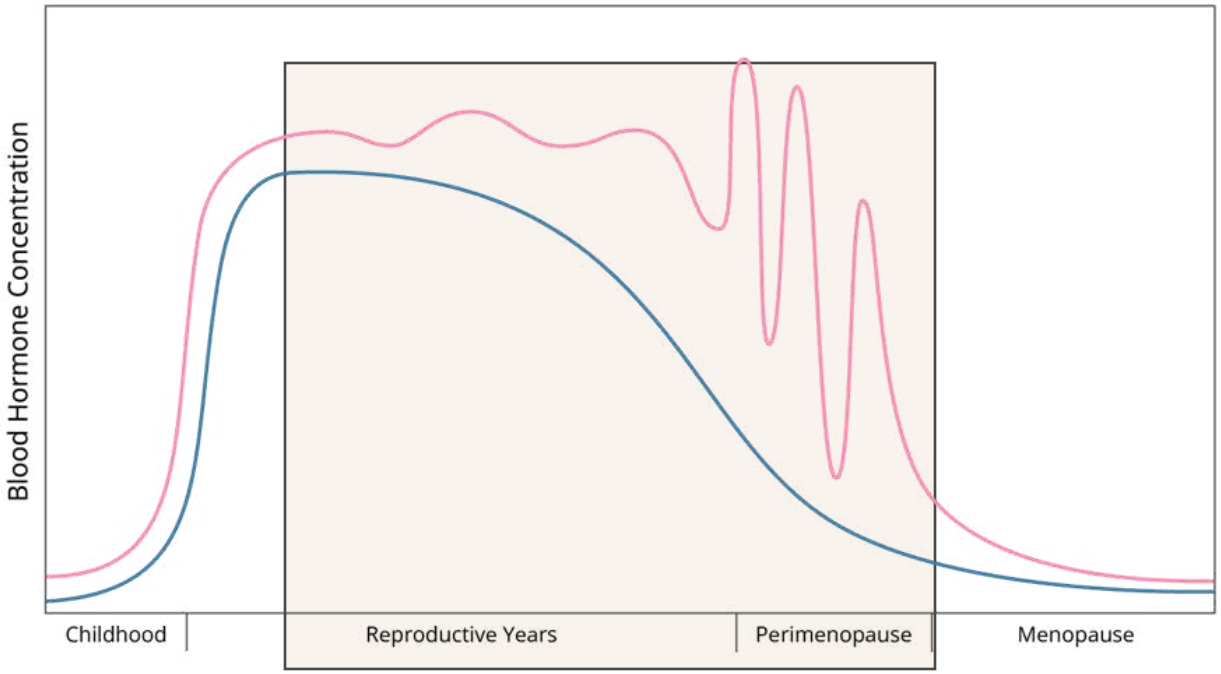
- Low Testosterone:
  - Anxiety, depression, diminished libido

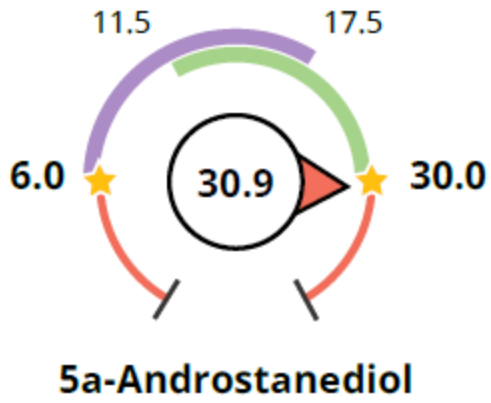


High Testosterone Levels in PreMP Females Indicated in Depression

- High Free Testosterone (5a-Androstanediol) in females
  - Depression in obese patients with high T
  - Depression in late perimenopause when T is high compared to low E2

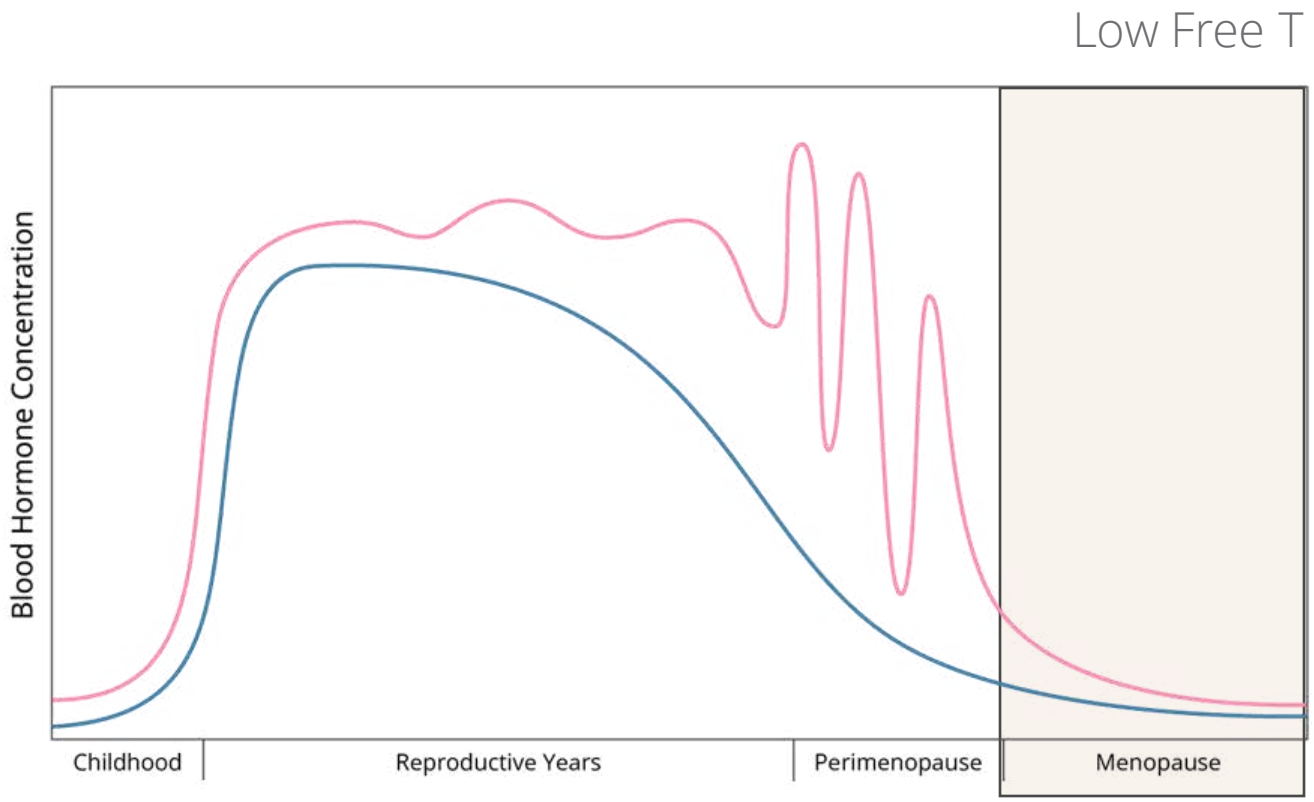
High Free T in obesity and in late peri

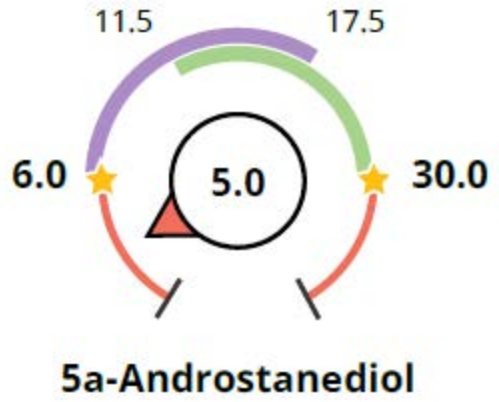




Low Testosterone Levels in PMP Females Affects Mood

- Low Free Testosterone (5a-Androstanediol) in females
  - Low testosterone: Anxiety, depression in postmenopausal females, diminished libido



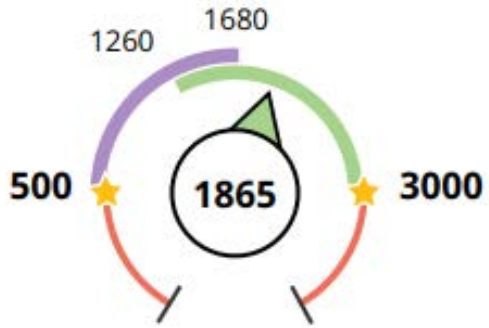


Both High and Low DHEA Levels Affect Mood

- High DHEA → High stress response
  - Anxiety
  - Depression (especially females, adolescents and obese)
  - Irritability

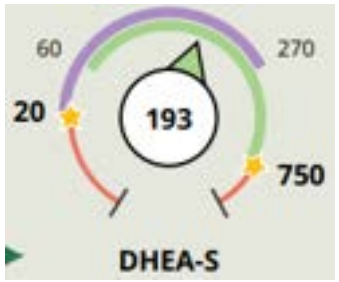
- Low DHEA → Inadequate stress response, associated with prolonged/chronic stress (especially in presence of low/flattened cortisol)
  - Brain fog
  - Depression (especially in presence of high cortisol; postmenopausal females and males)
  - Diminished libido and sense of well-being

Total DHEA Production = Calculated Value Captures DHEA-S Seen by Tissues

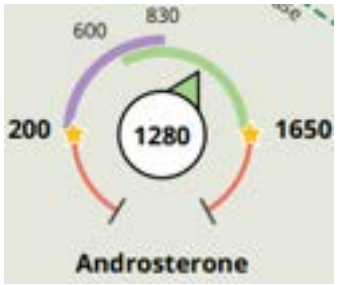


Luteal Range Postmenopausal Range Out of Range Edge of Range

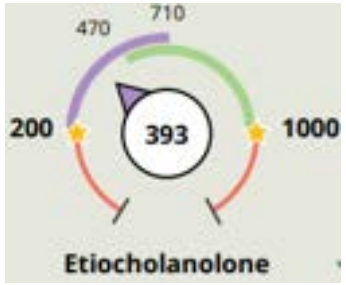
Ages 18 - 40 Ages 56 - 70



Sulfated



5a-Reductase



5b-Reductase

DHEA levels can be indicative of several things:

- High levels:
  - Adrenal Stress (acute)
  - Age (younger - declines with advancing age)
  - Athlete
  - Immune Activation
  - Inflammation (when DHEA-S is low compared to Androsterone and Etiocholanolone)
  - Insulin resistance
  - PCOS
  - Prolactin elevation

- Low levels:
  - Adrenal Stress (chronic)
  - Age (older - declines with advancing age)
  - Immune (chronic unresolved)
  - Inflammation (chronic unresolved)
  - Glucocorticoid use

Approach to Low Androgens

- Resistance Training
- Restore proper cortisol metabolism esp if cortisol clearance rate (CCR) is low
  - Treat hypothyroid if present
  - Treat anemia if present
  - Increase dietary caloric intake if inadequate
- Androgen-supporting botanicals
  - Ashwagandha, Fenugreek, Maca, Shatavari, Smilax, Tribulus
- DHEA supplementation
  - Physiologic dosing range 2.5-25mg
  - Supraphysiologic dosing range up to 450mg in published literature
  - Even physiologic doses of DHEA can raise **testosterone** and **estrogen** in postmenopausal females and in males
    - Periodically monitor testosterone and E2 in serum with use of oral DHEA
- Testosterone therapy (males and females)
- Mitochondrial supports
  - CoQ10, ALA, Carnitine, Pregnenolone, Magnesium, NAD+, etc

Approach to High Androgens

- Aerobic Training
- Restore proper cortisol metabolism esp if CCR is too high:
  - Increase insulin sensitivity
    - Herbs: Berberine, Bitter melon, Chamomile, Cinnamon, Curcumin, EGCG
    - Nutrition: R-ALA, Chromium, Myoinositol, Vanadium
- Support stress response
  - Adaptogenic botanicals
- Control prolactin if high with high DHEA
  - Rule out prolactinoma
  - Treat high TSH if present
  - Drugs: Cabergoline, Bromocriptine
  - Herbs: Vitex, Mucuna pruriens, Licorice
- Use anti-androgens
  - Herbs: Curcumin, DIM, EGCG, Licorice, Nettle Rt, Reishi, Saw Palmetto, White peony
  - Progesterone

Oxidative Stress and Neuroinflammation Contribute to Depression

Oxidative Stress Can Induce Depression:

- Increases cortisol production
- Pulls tryptophan away from 5-HT production → low Serotonin → low Melatonin
- Oxidizes tryptophan into pro-inflammatory products → high Quinolinate
- High Quinolinate acts as a neurotoxin → high Glutamate activity/excitotoxicity
- Increases the need for Glutathione → high Pyroglutamate
- Damages cellular structures including DNA → high 8-OHdG

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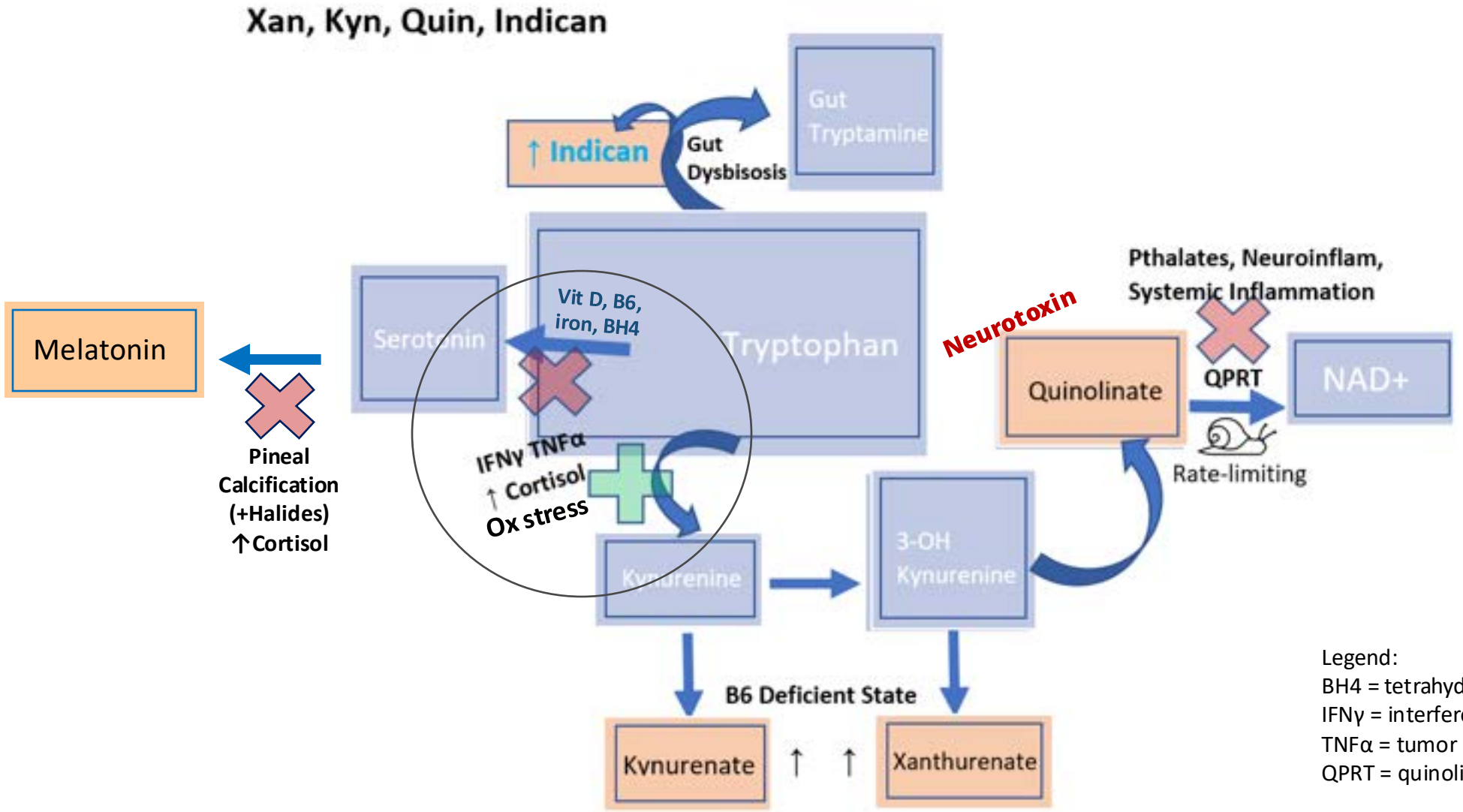
Identify 4 Oxidative Stress on a DUTCH Plus

- Oxidative Stress and ROS are indicated in bipolar disorder, depression, and schizophrenia
    1. Elevated 8OHdG
    2. Elevated Pyroglutamate
        1. Can also be a sign of deficiencies in glycine, NAC, B6, and C
    3. Elevated Cortisol Metabolites (and flattened free cortisol curve if chronic)
    4. Elevated or dominant 4-OHE1 and 4-OHE2 (Low 2-OHE1 : 4-OHE1 ratio)

- Treat using Antioxidants
    - Examples: Bioflavonoids (apigenin, citrus, hesperidin, quercetin, rutin), Liposomal Glutathione, NAC, Quercetin, Resveratrol, Sulforaphane, Vitamins/Minerals (A, C, D, E, Magnesium, Selenium, Zinc)

Oxidative Stress Leads to Neuroinflammation Through the Kynurenate Pathway

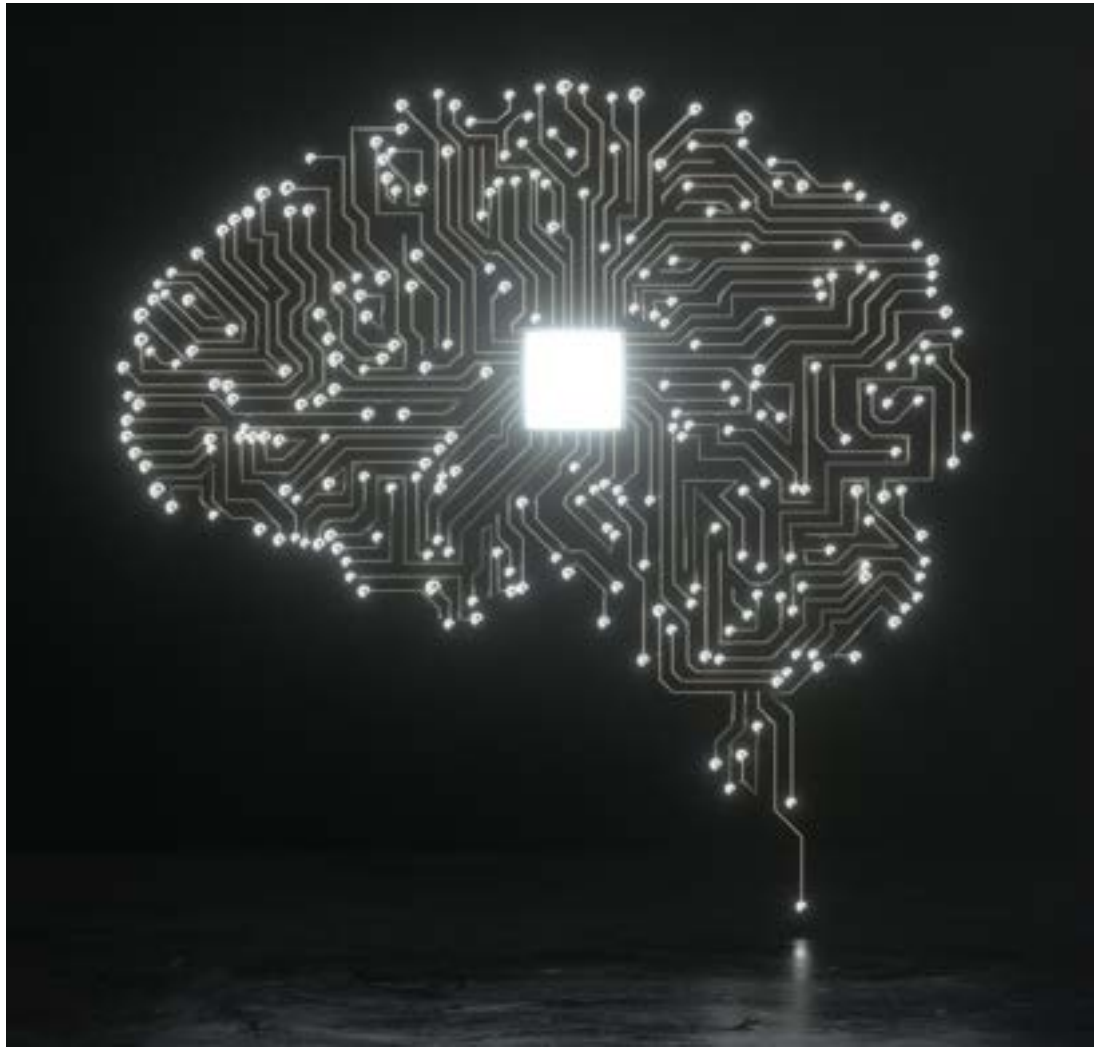
Tryptophan Pathway Shows Oxidative Stress Progression to Neuroinflammation



Legend:
BH4 = tetrahydrobiopterin
IFNγ = interferon gamma
TNFα = tumor necrosis factor alpha
QPRT = quinolinate phosphoribosyltransferase

Identify 4 Signs of Neuroinflammation on a DUTCH Plus

- High Quinolinate
  - Neurotoxin, sign of neuroinflammation, high excitatory activity, and high cortisol
- High Kynurenate
  - Neuroprotective but a sign of neuroinflammation and high cortisol when high
  - Low Kynurenate may also be a sign of low serotonin according to some studies
- High Cortisol
  - Abnormal diurnal pattern and/or CAR
  - High cortisol clearance rate (CCR)
- Low Melatonin
  - Linked with low serotonin
    - Tryptophan → Serotonin → Melatonin
  - Low melatonin also from chronic gut-brain axis dysfunction, inflammation, sleep problems and "light at night" influence on mental health
  - High melatonin: Sign of acute chronic gut-brain axis dysfunction/gut inflammation possibly (not well studied, theoretical)

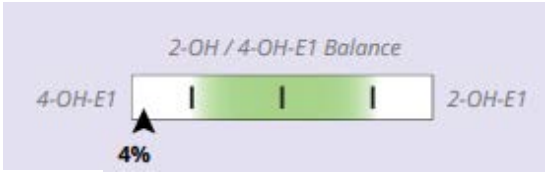


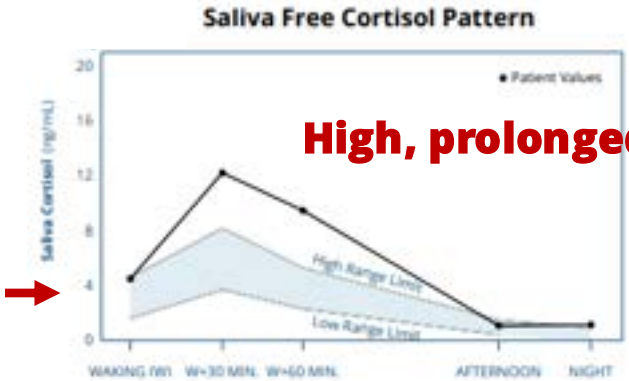
What signs of Oxidative Stress and Neuroinflammation do you see here?

Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Within range	2.1	ug/mg	0 - 3.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Within range	0.53	ug/mg	0.2 - 1.9
Kynurenate	Within range	2.9	ug/mg	1 - 6.6
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	9.3	ug/mg	0 - 18
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Above range	169.8	ug/mg	38 - 83
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Within range	92.5	ug/mg	0 - 131
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	5.4	ug/mg	4 - 16
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	3.1	ug/mg	2.5 - 7.5
Neuroinflammation Marker				
Quinolinate	Above range	13.3	ug/mg	0 - 12.5
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Below range	9.6	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	3.3	ng/mg	0 - 8.8

Low 2-OH-E1/4-OH-E1 ratio





High, prolonged CAR

High free cortisol sum

Neuro Anti-Inflammatory Therapeutics examples:

- Bacopa monnieri
- Citicoline
- Curcumin
- Estradiol therapy
- Ginkgo biloba
- Glutathione
- Glycine
- Gotu kola
- 5-HTP
- Lion’s Mane
- Melatonin
- Minerals (Lithium, Magnesium, Zinc)
- N-acetyl-cysteine (NAC)
- NADH
- Phosphatidylserine
- Probiotics (including Spores)
- Progesterone therapy
- Testosterone therapy

Tips on Supporting Melatonin

- Direct replacement approach:
  - Big dosing range, 3 sub-ranges
    - Low range 0.3 – 3mg studied for sleep
    - Mid range 3 – 10 mg studied for metabolic syndrome and inflammation
    - High range 20 mg+ studied for anti-tumor, estrogen modulation
    - Exercise caution in patients with suspected MTNR1b snp → may have increased risk of low-insulin diabetes with melatonin supplementation
- Serotonin-supportive approach (always increase monitoring if using with SSRI or SNRIs):
  - Tryptophan, 5-HTP, B6, Vitamin D
  - Herbs: Rhodiola, Passion flower, Curcumin, Bacopa, Saffron
- Keep cortisol in check at night
  - Adaptogens, Phosphatidylserine, L-Theanine, DHA (docosahexaenoic acid)
- Pineal gland supports
  - Antioxidants, avoidance of fluoride in some cases of calcification
- Employ good sleep hygiene practices and diurnal supports

Nutritional Deficiencies

Deficiencies Affecting Mental Health – Vitamin B6

- B6 Deficiency
  - Negatively Impacts
    - Serotonin synthesis
    - Dopamine synthesis
    - COMT enzyme activity (to clear Epinephrine when a stressor is resolved)
    - Glutathione recycling (increases Pyroglutamate)

- Signs of B6 Deficiency on DUTCH
  - Elevated Kynurenate and Xanthurenate
  - High Kynurenate particularly is indicative of neuroinflammation when Quinolinate is also high
    - Neuroinflammation → Neuroexcitatory → Depression

Vitamin B6 Markers - May be deficient if high				
→ Xanthurenate	Above range	1.30	ug/mg	0.12 - 1.2
→ Kynurenate	Above range	4.5	ug/mg	0.8 - 4.5

Deficiencies Affecting Mental Health – Vitamin B12

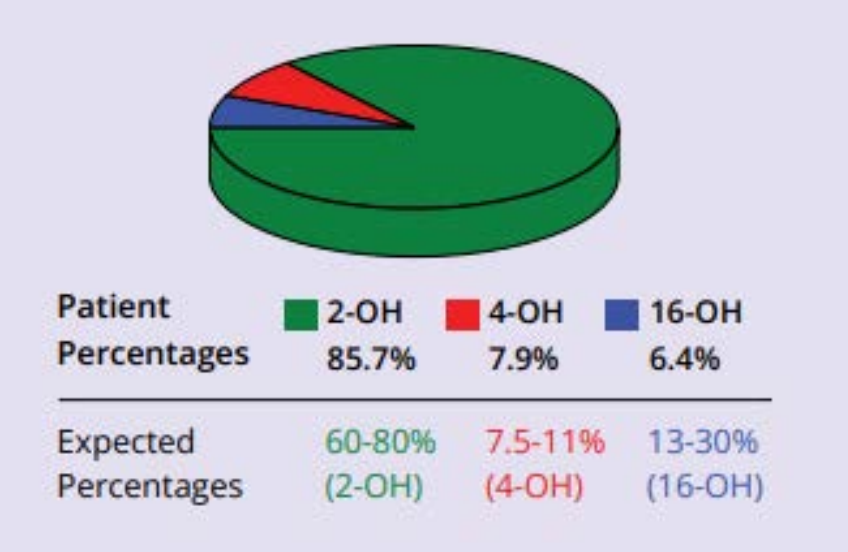
- Elevated MMA
  - Adenosyl-B12 deficiency
    - Decreases SAMe recycling → lowers COMT activity → reduced EPI clearance → inc stress impact
    - B12 often used as an augmentation therapy to antidepressants, especially in partial- and non-responders.

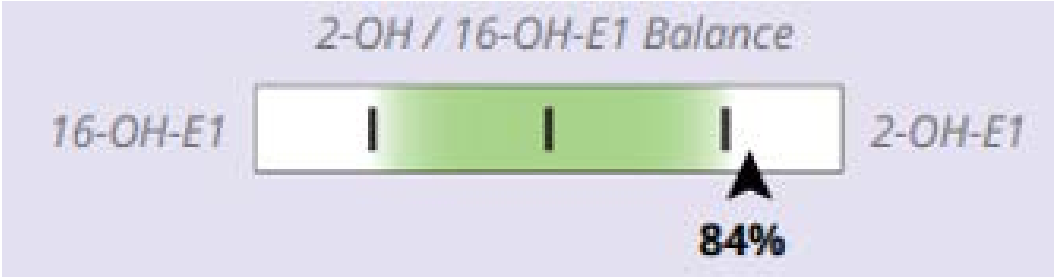
TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Above range	3.2	ug/mg	0 - 2.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Within range	0.47	ug/mg	0.12 - 1.2
Kynurenate	Within range	3.1	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	8.5	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Within range	45.8	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Within range	24.6	ug/mg	0 - 100

Sangle P, et al. Vitamin B12 Supplementation: Preventing Onset and Improving Prognosis of Depression. Cureus. 2020.

Deficiencies Affecting Mental Health – Vitamin D

- Low 16-OHE1 as compared to 2-OHE1 (aka **High 2:16 ratio**)
  - Check for low Vitamin D (25-OH-VitaminD is endogenous inducer of CYP3A4)





Can be a sign of D deficiency

Gut Microbiome Connection

Microbiome Link to Mental Health

Dysbiosis → HPA axis dysfunction and loss of hippocampal volume → Depression

"Dysbiosis can result in chronic alterations in the HPA axis, impairing axis regulation and chronic excess cortisol in the circulation. Excess cortisol can culminate in neuroinflammation and brain changes, such as reduced neuronal plasticity, decreased brain-derived neurotrophic factor (BDNF) levels, and atrophy. All these changes are mostly present in the hippocampus and prefrontal cortex and contribute to cognitive deficits, depressive symptoms, and impaired adaptation to stress."

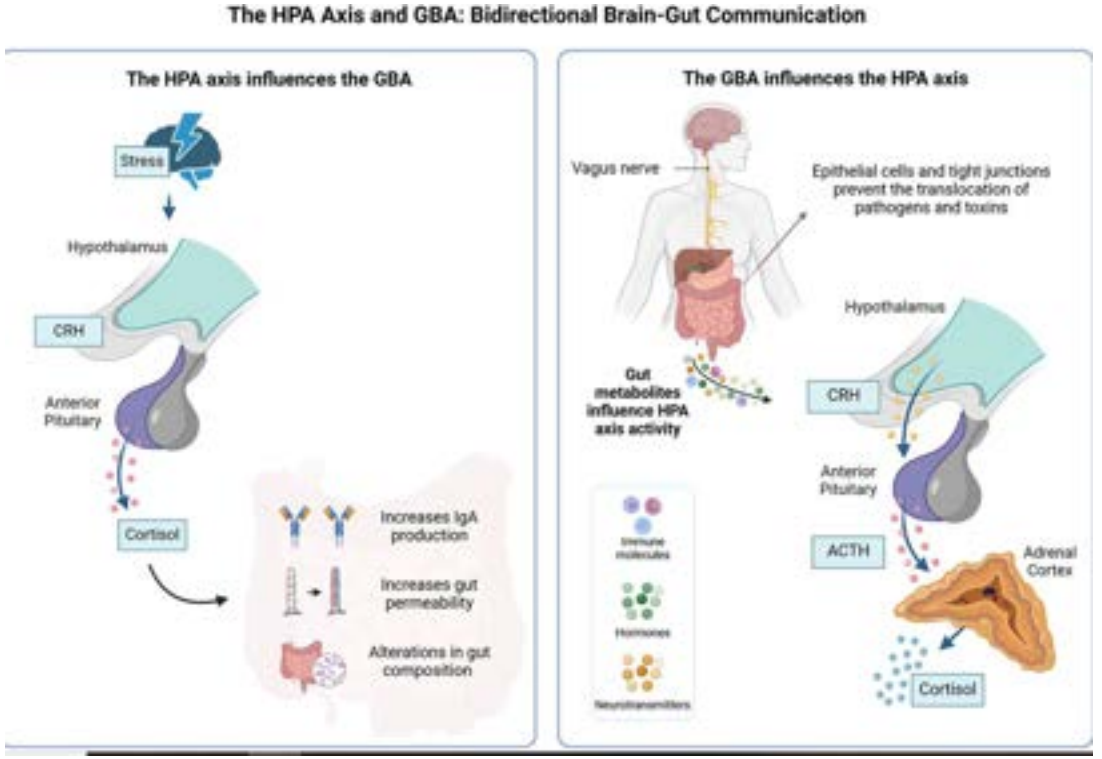


Figure 3

Bertollo AG, et al. Frontiers in Neuroscience. 2025.

Signs of Gut Dysbiosis on a DUTCH Test

- High Indican
  - Elevated when indican-producing organisms predominate.
    - Bacteroides, Clostridia (some spp.), E. coli, Prevotella
  - Stool testing may be indicated when indican is high in the presence of a mental health diagnosis.
- High MMA
  - Elevated when B12 is low.
  - Can be a sign of malabsorption secondary to SIBO and gut inflammation.
- High Kynurenate
  - Elevated when B6 is low, in Proteobacteria overgrowth, and when neuroinflammatory processes are occurring.
- High B-Hydroxyisovalerate
  - Elevated when biotin is low.
  - Biotin deficiency can be a consequence of dysbiosis.

What signs of dysbiosis do you see?

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Kynurenate	Within range	3.5	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	9.6	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Within range	40.0	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Above range	107.4	ug/mg	0 - 100
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	5.9	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	4.1	ug/mg	2.2 - 5.5
Neuroinflammation Marker				
Quinolinate	Within range	6.7	ug/mg	0 - 9.6
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Within range	39.6	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	3.1	ng/mg	0 - 5.2

Probiotics Studied for Mental Health

- Bifidobacterium strains (including but not limited to: B. bifidum, B. lactis, B. longum)
  - Bifidobacteria spp increase SCFA formation (butyrate) which amplifies gut-brain axis support.
- Lactobacillus strains (including but not limited to: L. acidophilus, L. casei, L. helveticus, L. lactis, L. paracasei, L. plantarum, L. reuteri, L. rhamnosis, L. salivarius)
  - Lactobacillus regulate gut inflammation, neurotransmitter balance, and HPA axis function.
- Bacillus strains (B. coagulans – MTCC 5856 for IBS + MDD, B. licheniformus)
  - Bacillus strains increase SCFA formation and are anti-inflammatory in the gut.

Bottom Line for Neuro/Mental Health Presentations

- Probiotic Selection should include:
  - Lactobacillus component
  - Bifidobacterium component
  - Consider spore probiotics if IBS part of etiology
  - A prebiotic and/or fiber component
  - Antioxidant component
    - Consider esp when there are signs of oxidative stress on DUTCH

Summary of Contributors to Depression Found on a DUTCH Plus

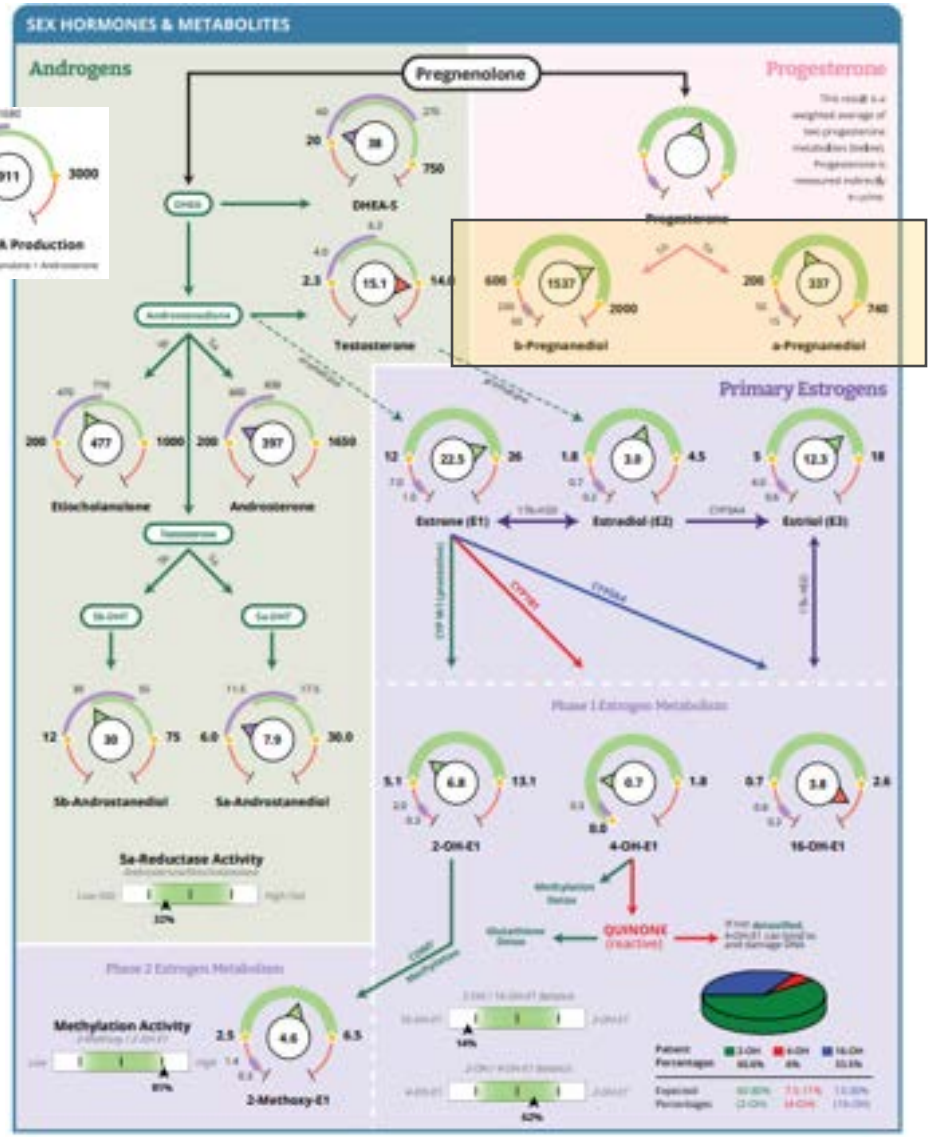
DUTCH Result	Cycling Female	Menopausal Female	Male
High Estradiol			X
Low Estradiol	X	X	
Low Progesterone	X	X	
High Testosterone	X		
Low Testosterone		X	X
High DHEA	X	X	X
Low DHEA	X	X	X
High Free Cortisol	X	X	X
Low Free Cortisol with High CCR	X	X	X
High or Low COMT	X	X	X
Oxidative Stress Markers	X	X	X
Neuroinflammation Markers	X	X	X
B6/B12 Deficiencies	X	X	X


How about a case study!

40yoF, Regular cycles, Anxiety and Depression

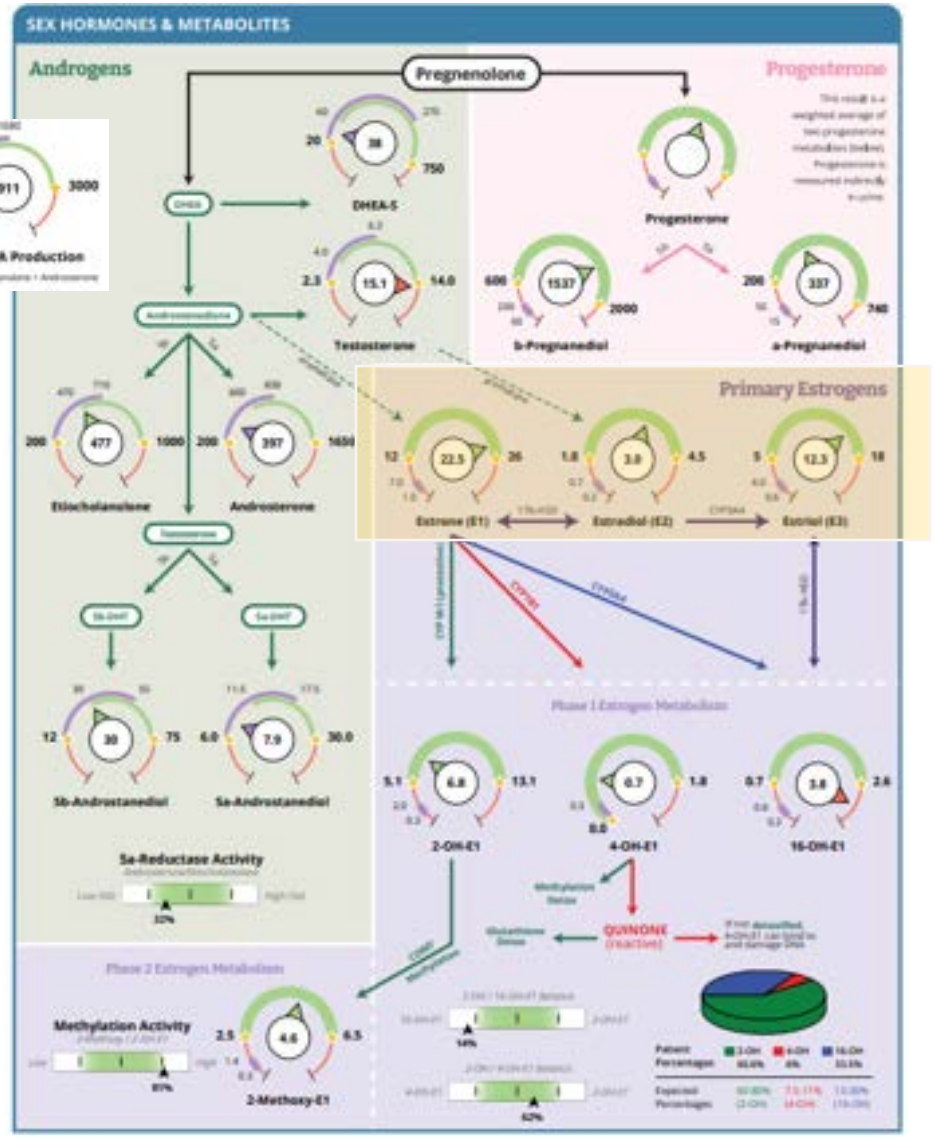
- In for integrative care assessment and co-management of depression.
- Persistent symptoms are low mood, sporadic anxiety, fatigue, difficulty sleeping, and since starting SNRI has decreased libido.
- Concerned that cortisol is high.
- Currently managed on an SNRI, a non-benzo anxiolytic, and a Z-drug for sleep.
- History of high inflammatory markers on past testing but was never offered treatment for it.

40yoF – Regular cycles, Anxiety and Depression



- Assessment:
  - Normal luteal PG metabolites
  - Normal parent estrogens
  - ↑ 16-OHE1 compared to 2-OHE1
    - (Low 2:16 ratio)
  - Normal 2:4 ratio
  - Fast COMT activity
  - High Testosterone
  - Low DHEA

40yoF – Regular cycles, Anxiety and Depression



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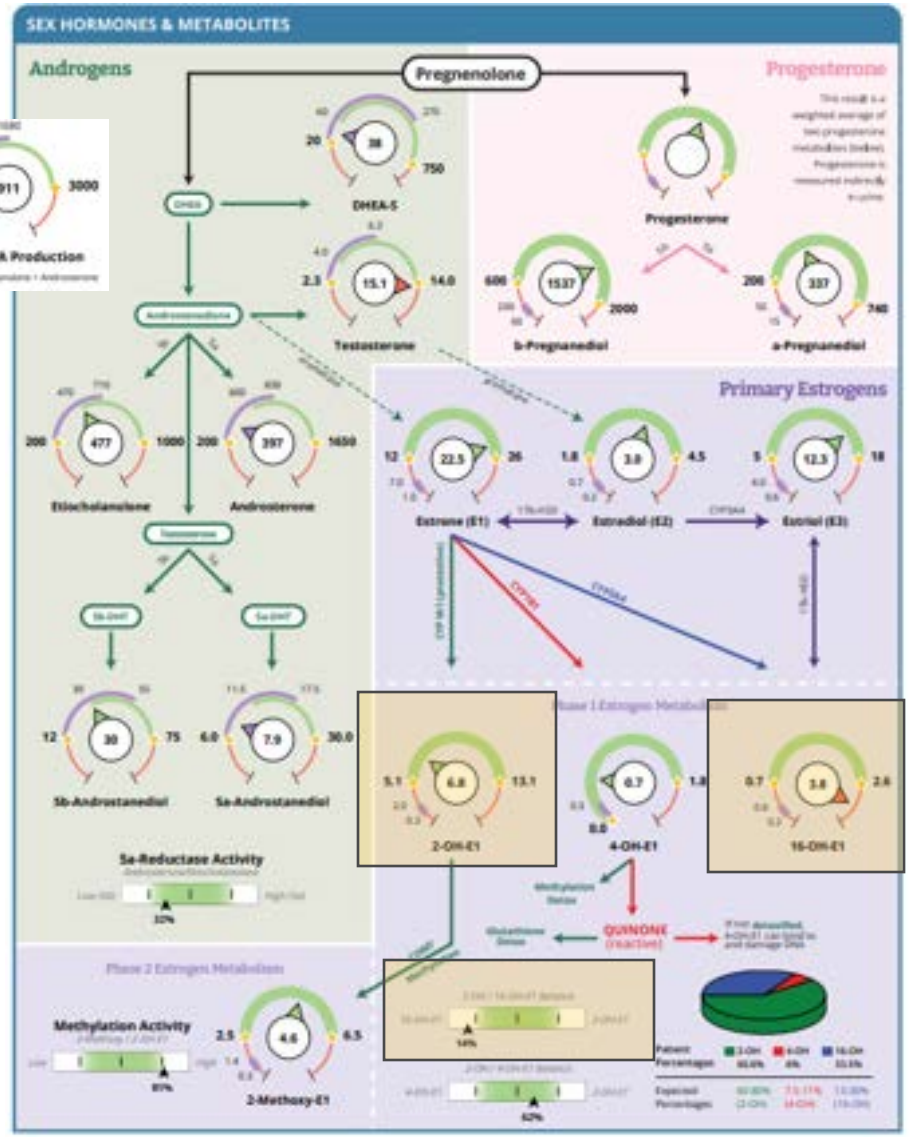

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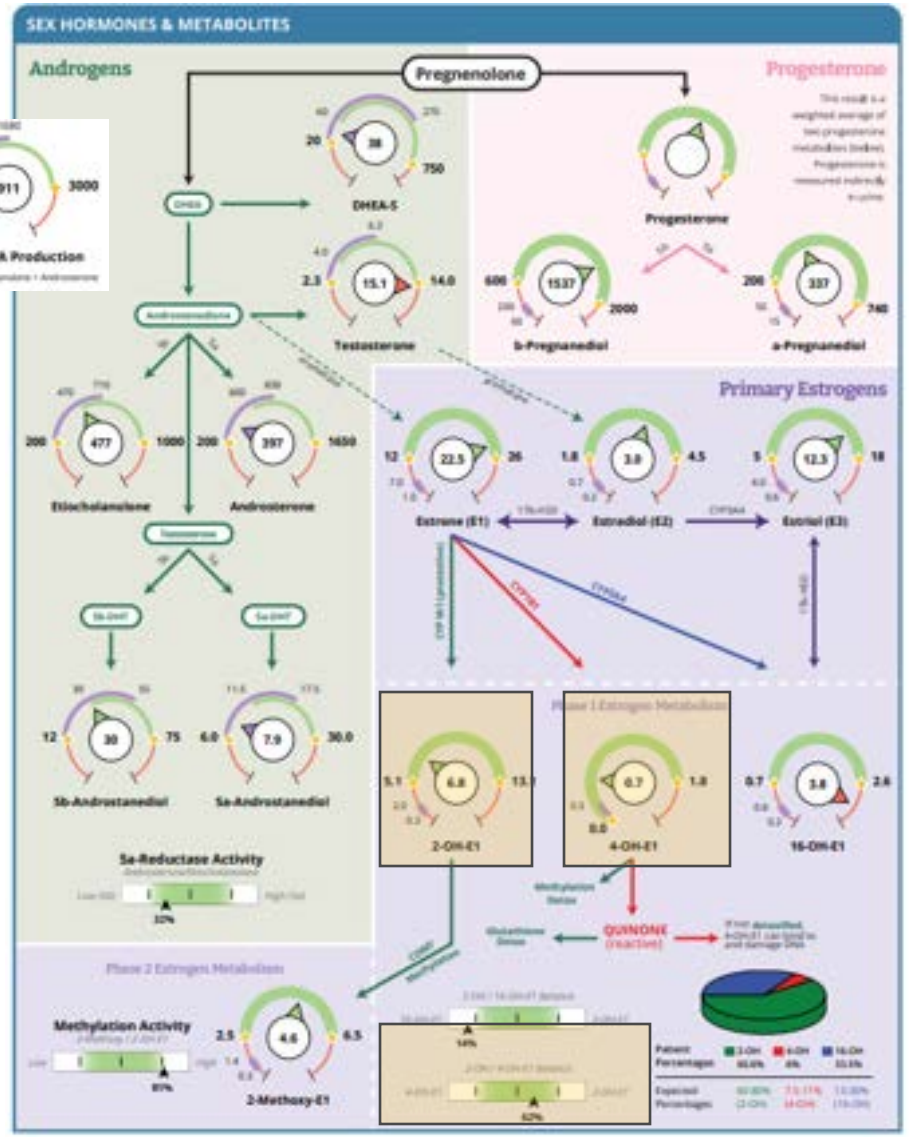
  - Low DHEA

- Causes of low 2:16 ratio in females: gut dysbiosis, obesity, alcohol, autoimmune….

40yoF – Regular cycles, Anxiety and Depression



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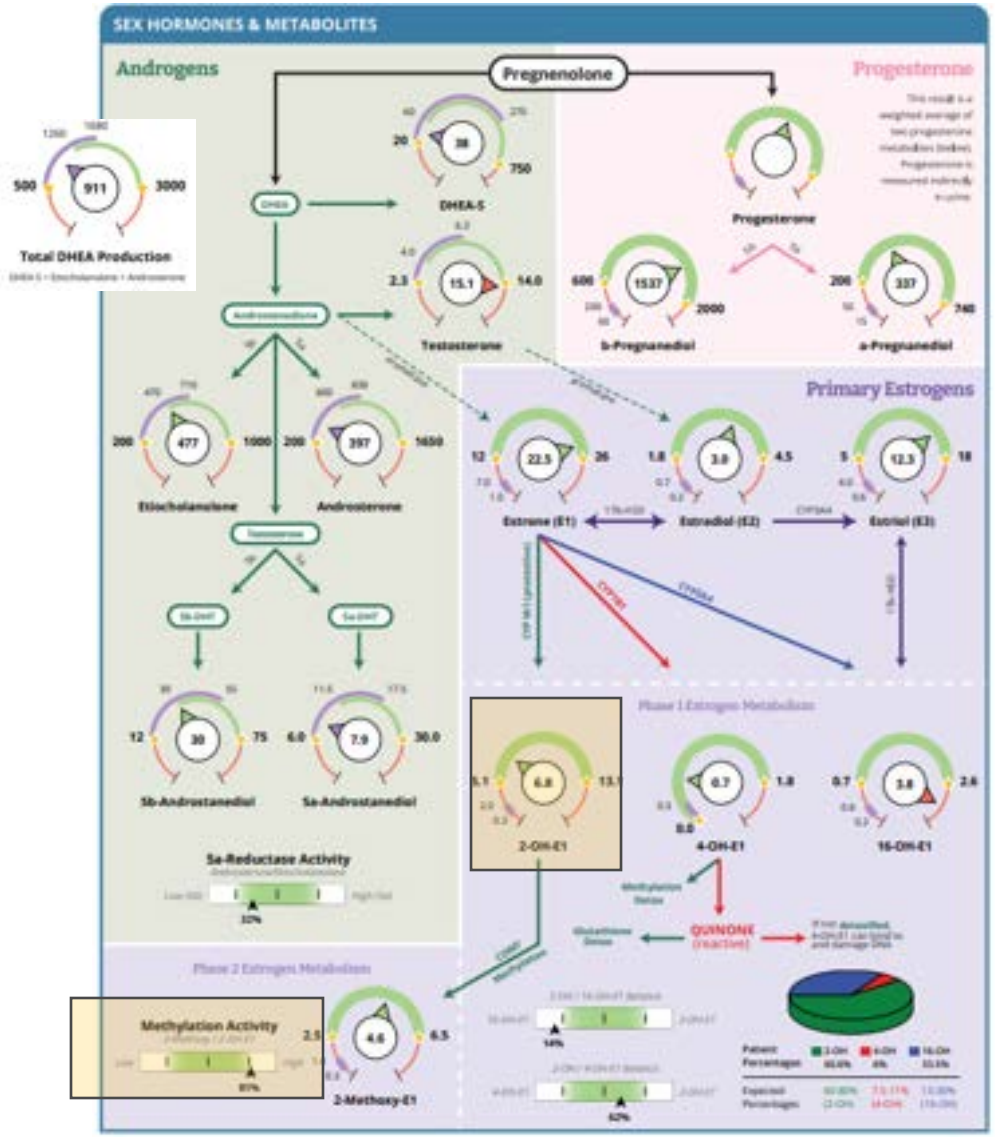
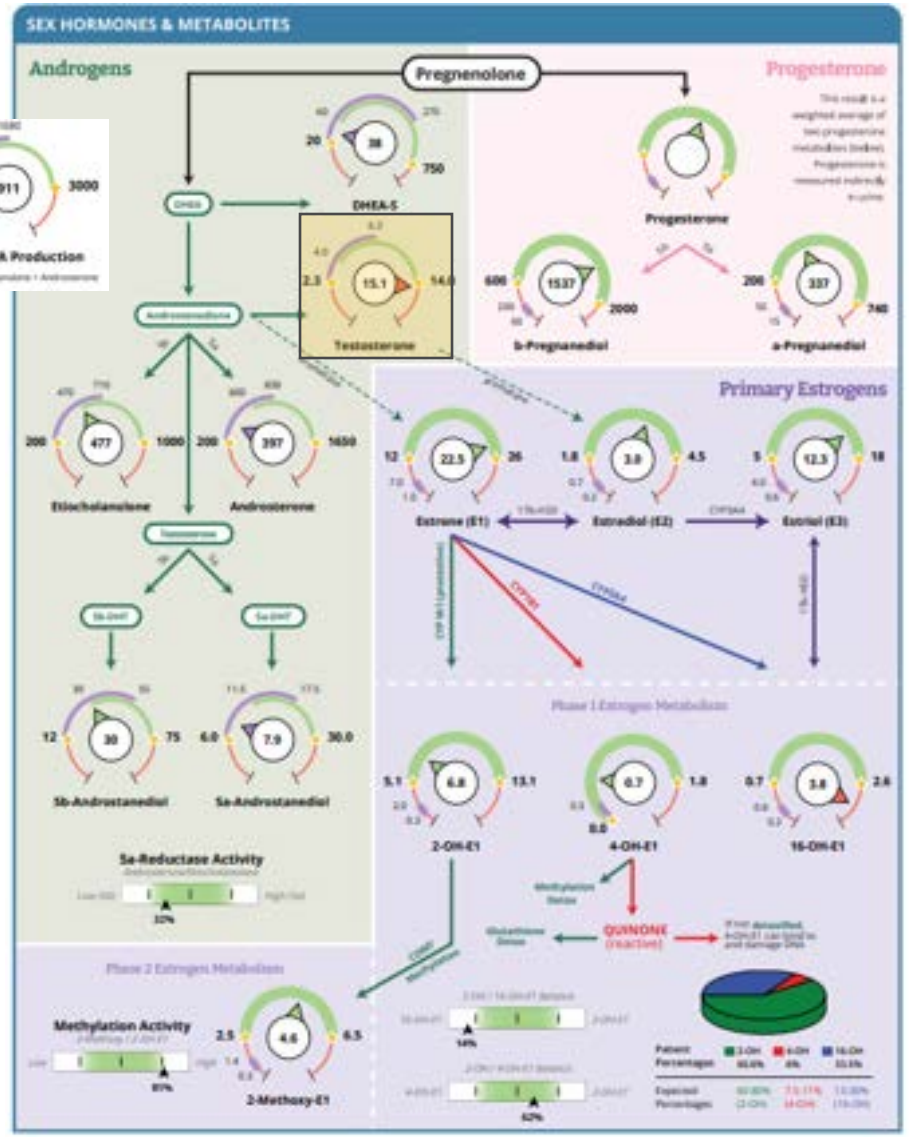
  - ↑ 16-OHE1 compared to 2-OHE1
    - (Low 2:16 ratio)
  - Normal 2:4 ratio
  - Fast COMT activity
  - High Testosterone
  - Low DHEA

40yoF – Regular cycles, Anxiety and Depression



- Assessment:
  - Normal luteal PG metabolites
  - Normal parent estrogens
  - ↑ 16-OHE1 compared to 2-OHE1
    - (Low 2:16 ratio)
  - Normal 2:4 ratio
  - Fast COMT activity
  - High Testosterone
  - Low DHEA

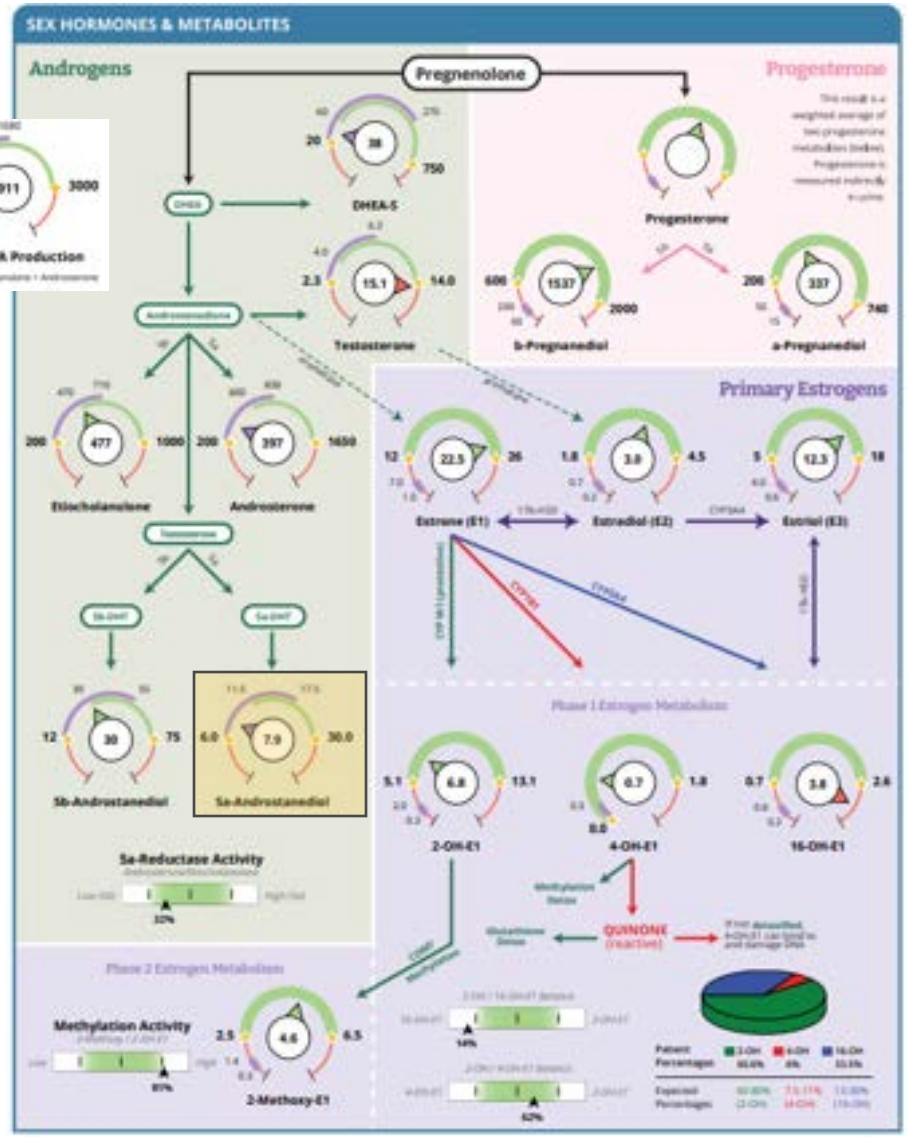
40yoF – Regular cycles, Anxiety and Depression



- Assessment
  - Testosterone high
  - 5a-Andro is low for age
  - Total DHEA Production is low for age
  - DHEA –S is low for age
  - Androsterone is low for age

- Causes of high T in females: inflammation, insulin resistance, high LH, gut dysbiosis….

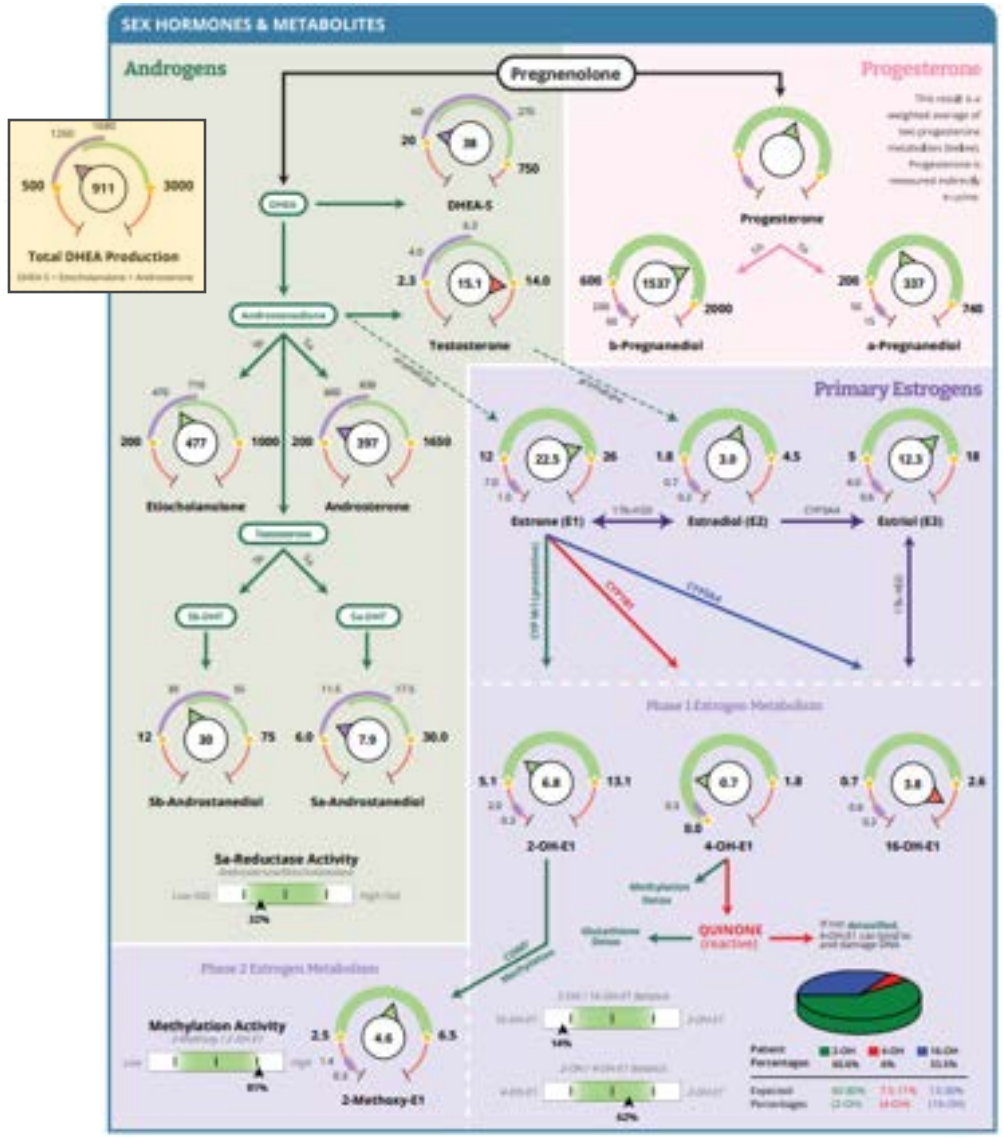
40yoF – Regular cycles, Anxiety and Depression



- Assessment
  - Testosterone high
  - 5a-Andro is low for age
  - Total DHEA Production is low for age
  - DHEA –S is low for age
  - Androsterone is low for age

- Low androgenic activity from testosterone at tissue level

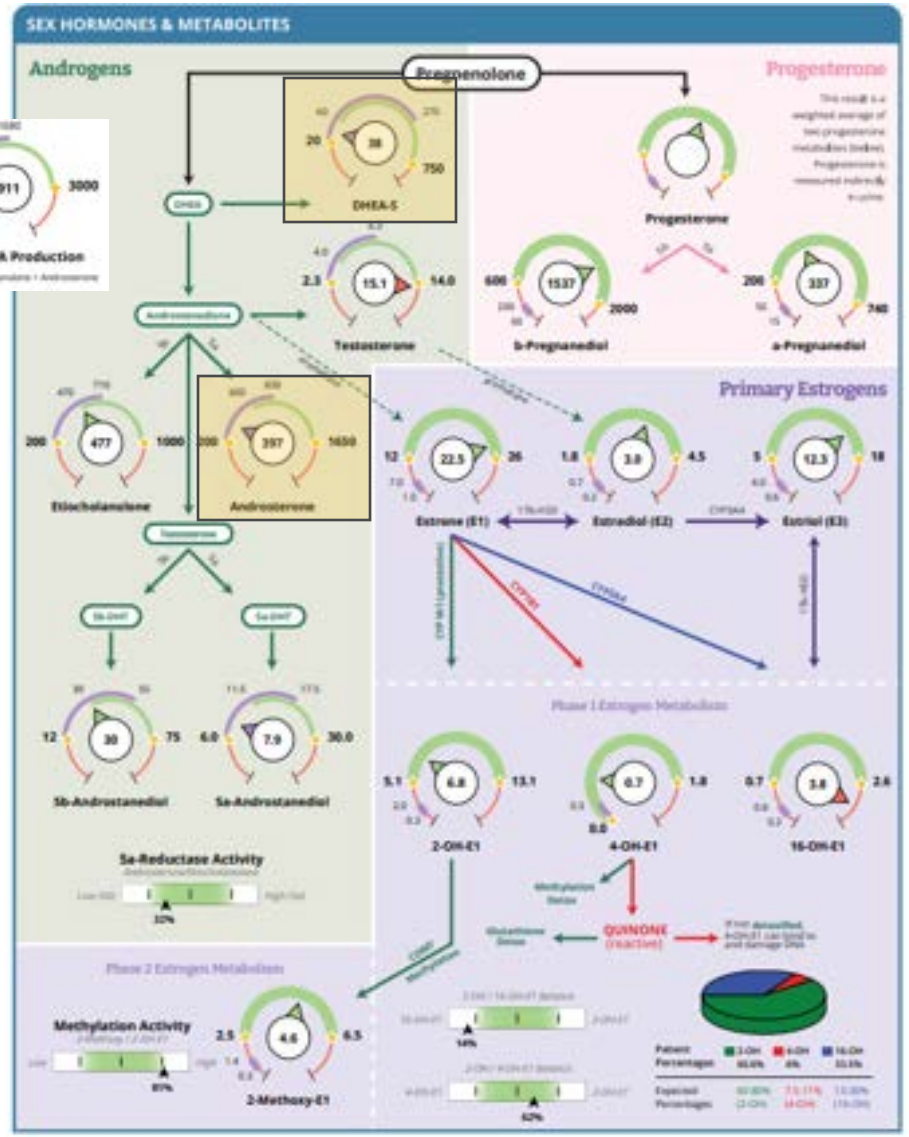
40yoF – Regular cycles, Anxiety and Depression



- Assessment
  - Testosterone high
  - 5a-Andro is low for age
  - Total DHEA Production is low for age
  - DHEA –S is low for age
  - Androsterone is low for age

- Low DHEA suggests chronic stressors and inflammation.

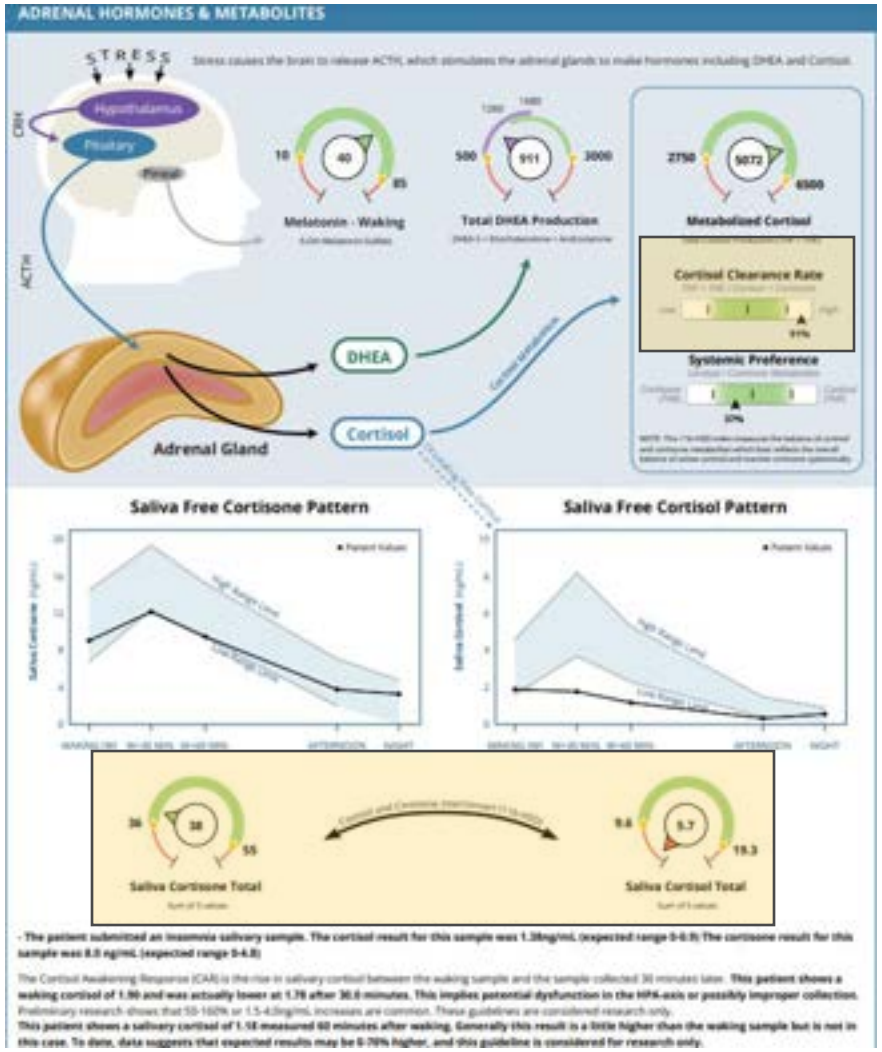
40yoF – Regular cycles, Anxiety and Depression



- Assessment
  - Testosterone high
  - 5a-Andro is low for age
  - Total DHEA Production is low for age
  - DHEA –S and Androsterone both low for age

- Confirms low DHEA activity within tissues

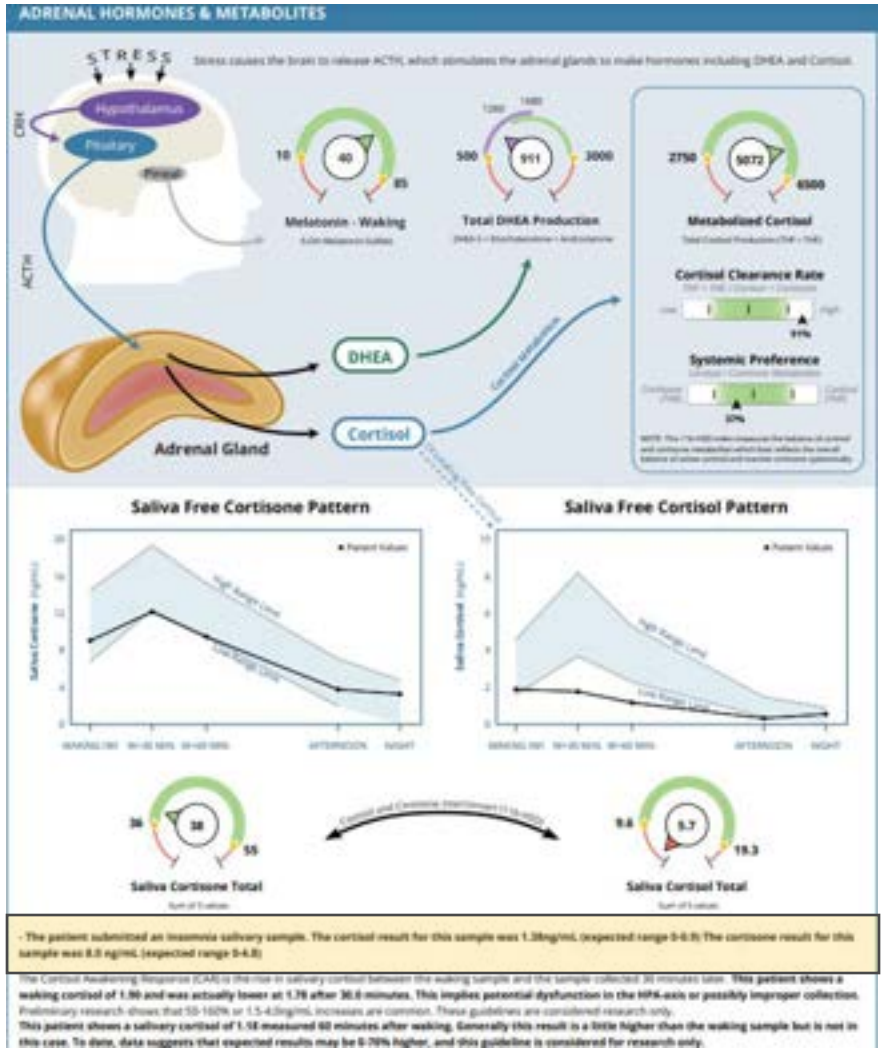
40yoF – Regular cycles, Anxiety and Depression



- Assessment:
  - Free cortisol (and cortisone) sums are low to low-normal at best
    - Cortisol Clearance Rate is too fast
  - 1:40 am Free cortisol elevated
  - Diurnal slope is flat
  - CAR is low/absent
  - DHEA is low
  - Melatonin is normal

- Fast CCR is seen in inflammation, insulin resistance, and immune activation

40yoF – Regular cycles, Anxiety and Depression



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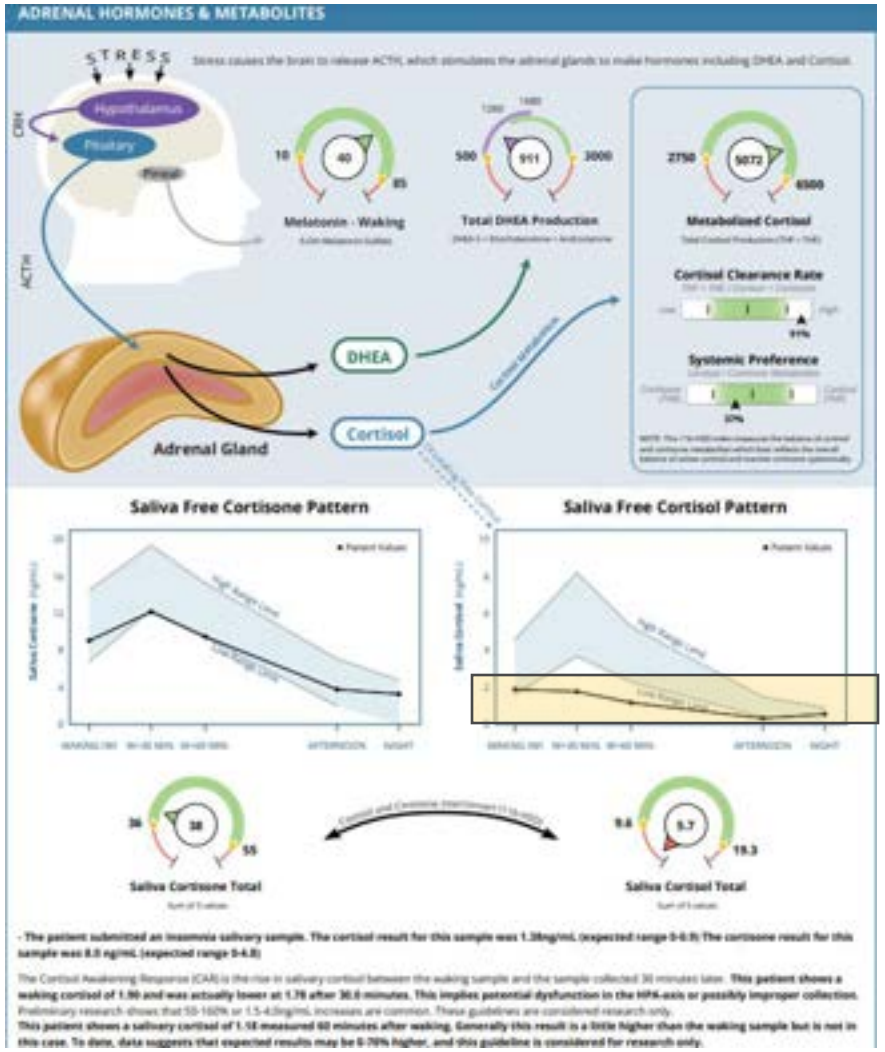
40yoF – Regular cycles, Anxiety and Depression



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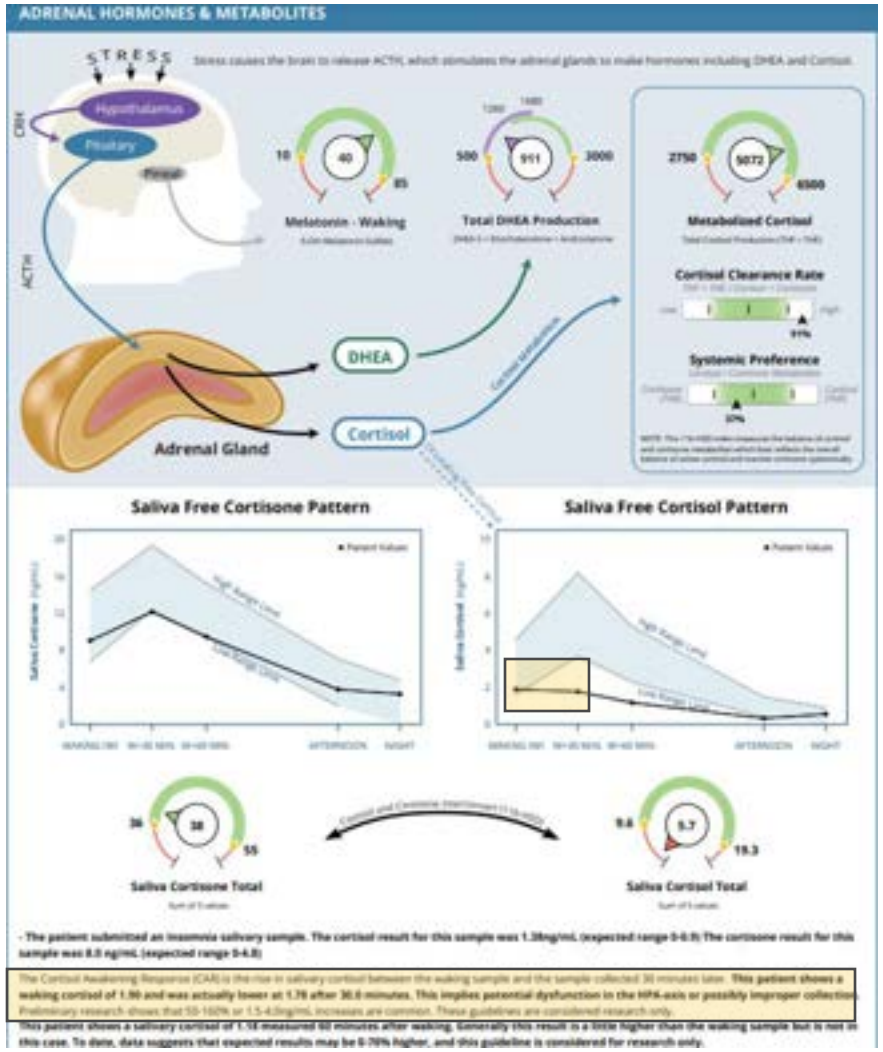
40yoF – Regular cycles, Anxiety and Depression



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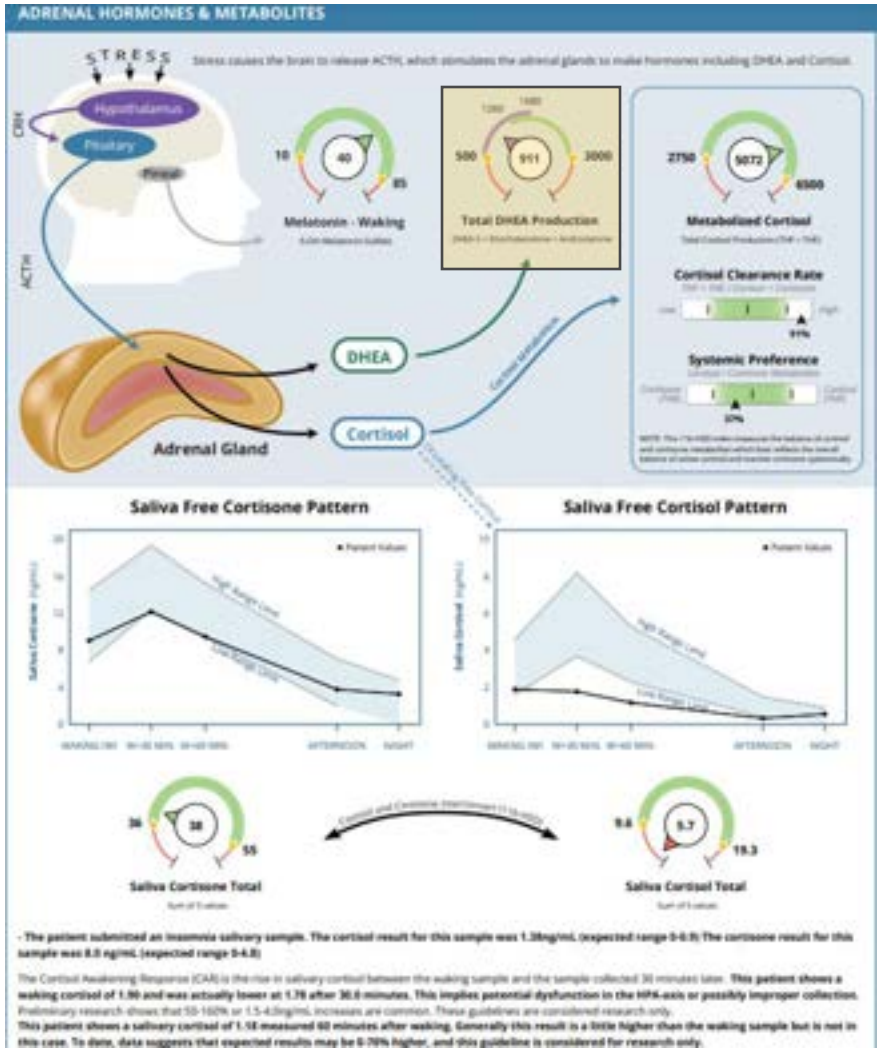
  - DHEA is low
  - Melatonin is normal

- Flat diurnal curve + high night cortisol + low CAR is consistent with chronic inflammation

40yoF – Regular cycles, Anxiety and Depression



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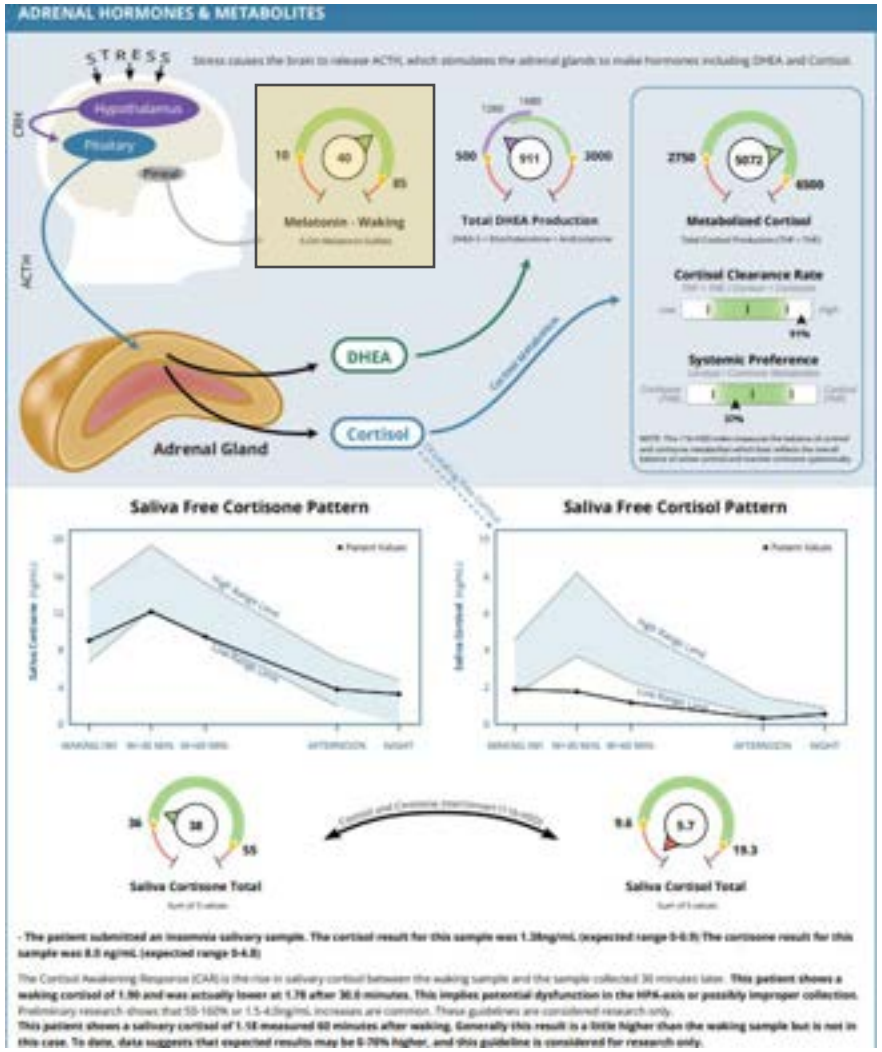
  - DHEA is low
  - Melatonin is normal

- Low DHEA is consistent with chronic inflammation

40yoF – Regular cycles, Anxiety and Depression



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40yoF – Regular cycles, Anxiety and Depression

Organic Acid Tests (OATs)

TEST		RESULT	UNITS	NORMAL RANGE
Nutritional Organic Acids (Urine)				
Vitamin B12 Marker - May be deficient if high				
Methylmalonate (MMA)	Above range	3.6	ug/mg	0 - 2.5
Vitamin B6 Markers - May be deficient if high				
Xanthurenate	Within range	0.53	ug/mg	0.12 - 1.2
Kynurenate	Within range	3.5	ug/mg	0.8 - 4.5
Biotin Marker - May be deficient if high				
b-Hydroxyisovalerate	Within range	9.6	ug/mg	0 - 12.5
Glutathione Marker - May be deficient if low or high				
Pyroglutamate	Within range	40.0	ug/mg	28 - 58
Gut Marker - Potential gut putrefaction or dysbiosis if high				
Indican	Above range	107.4	ug/mg	0 - 100
Neuro-Related Markers (Urine)				
Dopamine Metabolite				
Homovanillate (HVA)	Within range	5.9	ug/mg	3 - 11
Norepinephrine/Epinephrine Metabolite				
Vanilmandelate (VMA)	Within range	4.1	ug/mg	2.2 - 5.5
Neuroinflammation Marker				
Quinolinate	Within range	6.7	ug/mg	0 - 9.6
Additional Markers (Urine)				
Melatonin - Waking				
6-OH-Melatonin-Sulfate	Within range	39.6	ng/mg	10 - 85
Oxidative Stress / DNA Damage				
8-Hydroxy-2-deoxyguanosine (8-OHdG)	Within range	3.1	ng/mg	0 - 5.2

- Assessment:
  - High Indican
    - Gut dysbiosis and/or maldigestion is a contributing factor to 16-OH-E1 dominance and low B12.
  - Low Adenosyl-B12

40yoF – Regular cycles, Anxiety and Depression

Organic Acid Tests (OATs)

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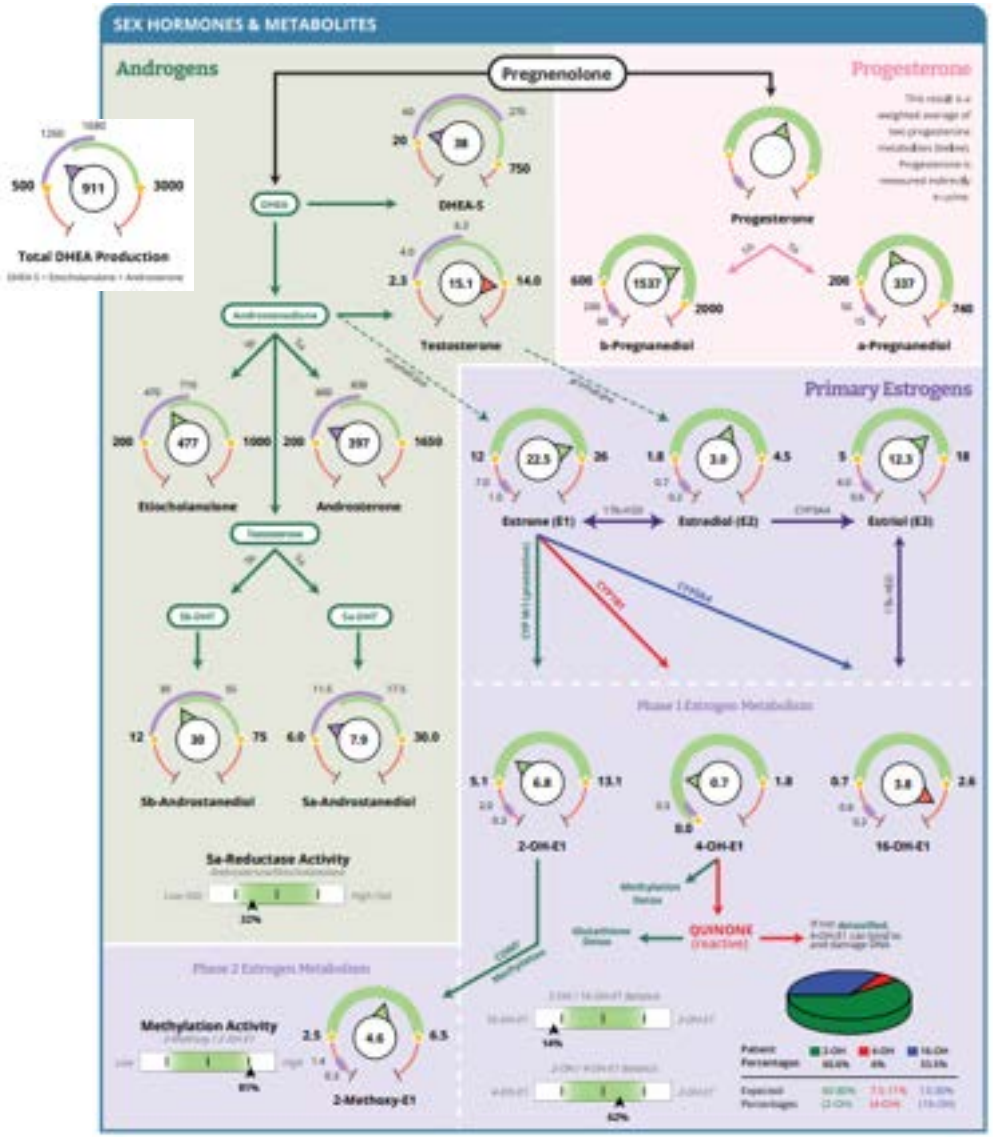
- Assessment:
  - High Indican
    - Gut dysbiosis and/or maldigestion is a contributing factor to 16-OH-E1 dominance and low B12.
  - Low Adenosyl-B12

- Dysbiosis and deficiencies may contribute to incomplete response to SNRI

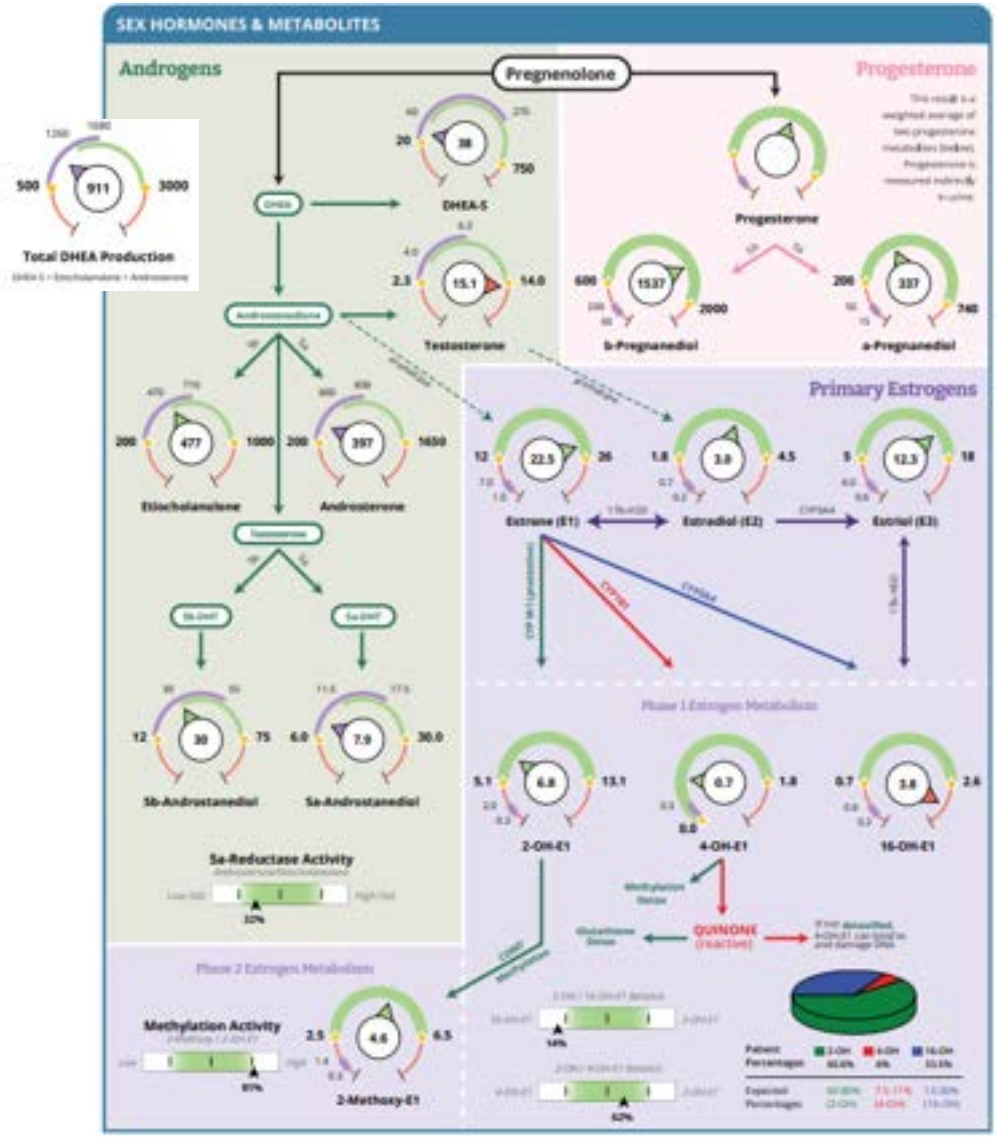
40yoF – Regular cycles, Anxiety and Depression



Example Plans for Estrogens (incorp OATs):

- Phase 3 support:
  - Order Comprehensive Stool test for tailored approach to gut healing (16-OHE1, Indican, and MMA)
- Phase 2 COMT tempering:
  - Trans-resveratrol, Quercetin
  - Hydroxo/Adenosyl-B12 combo daily titrating from low doses as add-on therapy to SNRI
- Phase 1 support:
  - DIM 200 mg daily or trans-Resveratrol + Sulforaphane as bridge therapy until microbiome health is restored

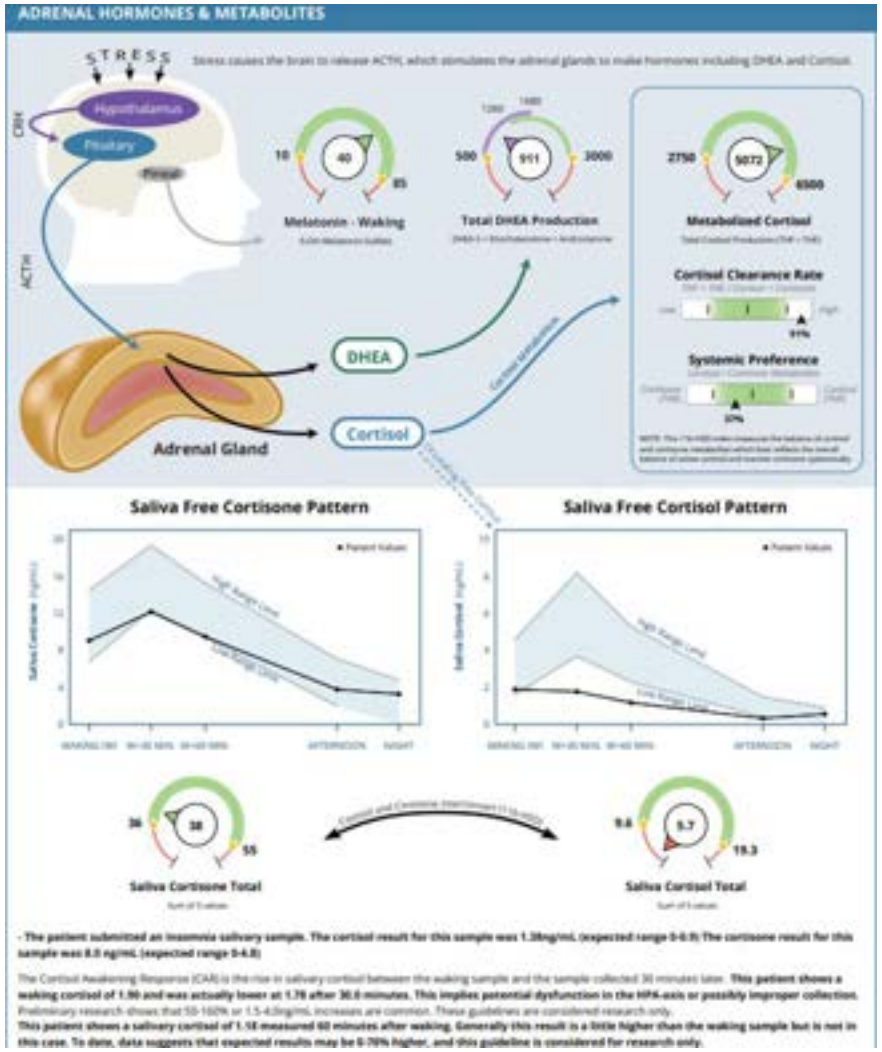
40yoF – Regular cycles, Anxiety and Depression



Example Plan for the Androgens:

- Testosterone high but 5a-Andro is low for age
  - T likely coming more from ovarian source since DHEA is low – inflammation?
  - Defer direct treatment in favor of treating indirectly with anti-inflammatory protocol
- Save DHEA plan for Adrenal section
  - Uniform low DHEA-S, Androsterone, and Etiocholanolone suggests Chronic Inflammation etiology.

40yoF – Regular cycles, Anxiety and Depression



- **Example Plan for Adrenals**
  - Flat slope, low CAR, high night cortisol, and high CCR = Chronic Inflammation
    - Use anti-inflammatory protocol
      - Curcumin (choose a high absorption type, dose depends on type) – titrate
      - Saffron 3.5% 14 mg QD-BID
      - Consider use with other anti-inflammatory adaptogens from slide 33.
  - Low DHEA
    - Use anti-inflammatories to restore production. See above ↑
    - Consider DHEA supplementation in the future if levels remain low with resolution of inflammation.

Initial Rx based on DUTCH Plus Test

1. Spend some time outside at least 3x a week for 10 min or more “Nature Pill”
2. Hydoxo/Adenosyl B12 combo sublingual 500 mcg/500 mcg, titrate to normalization
3. Mood Probiotic with Lactobacillus spp/Bifidobacterium blend + antioxidants 10 billion – 25 billion CFU
4. Slow COMT activity + decrease 16-OH-E1:
    1. Trans-Resveratrol/Quercetin combo
5. Anti-inflammatory nutraceuticals that also support neurotransmitter balance:
    - Curcumin Meriva © form: 500 mg BID
    - Saffron 3.5%: 14 mg QD-BID (and improve sexual side effects from SNRI*)

* Kashani L, et al. Hum Psychopharmacol. 2013;28(1):54-60.

Follow-Up

Order Comprehensive Stool Test to explore exact cause of high Indican and MMA for specific gut-centric treatment plan next visit

Order serum lab work to explore CBC, CMP, inflammatory and nutritional markers, thyroid panel, fasting insulin, and A1c to start.

Follow up in 3 weeks for interim symptoms assessment and review stool and serum test results

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That brings us to the end!

Or perhaps the beginning – happy testing!

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