



Clinical Pearls to Understanding Neurotransmitters for NeuroWellness and Using Them in Practice Tomorrow

R.W. « Chip » Watkins, MD, MPH, FAAFP

Your Speaker

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- Lab Director and President of NeuroLab, Inc.
- Lab Director and President of CommunityLab, Inc.
- Medical Director, Sanesco International, Inc.
- Board Member and AAFP Appointee to the COLA Board of Directors
- SGE and member of CDC's CLIAC (Clinical Laboratory Improvement Advisory Committee)
- Former President and Board Chair of the NC Academy of Family Physicians





Sanesco[®]

health in balance

Neuroendocrine
Laboratory

NeuroLab[®]
A Division of Sanesco International

Targeted
Neuroendocrine
Supplements



TARGETED
NUTRITIONAL THERAPY

Diagnostic
Laboratory



COMMUNITYLAB
a division of Sanesco Health

NeuroLab.

Proven Testing Methodologies

- Utilizes the gold standard technology for neurotransmitter analysis: UHPLC Triple Quadrupole Mass Spectrometry
- Highest level of sensitivity and specificity for neurotransmitters for the most accurate and reproducible results
- Every run is accompanied by a control
- Participates in voluntary, third-party, quality assurance testing



Webinar

Agenda

1. Understand the role neurotransmitters and hormones play in NeuroWellness and the presentation of clinical complaints by use of a case study
2. Utilize a neuroendocrine report to identify imbalances connected to clinical presentation
3. Employ a neuroendocrine report to develop personalized intervention strategies
4. Explore conventional and integrative strategies to balance neuroendocrine health and promote NeuroWellness
5. Implement a NeuroWellness Program in your practice
6. Question & Answer session

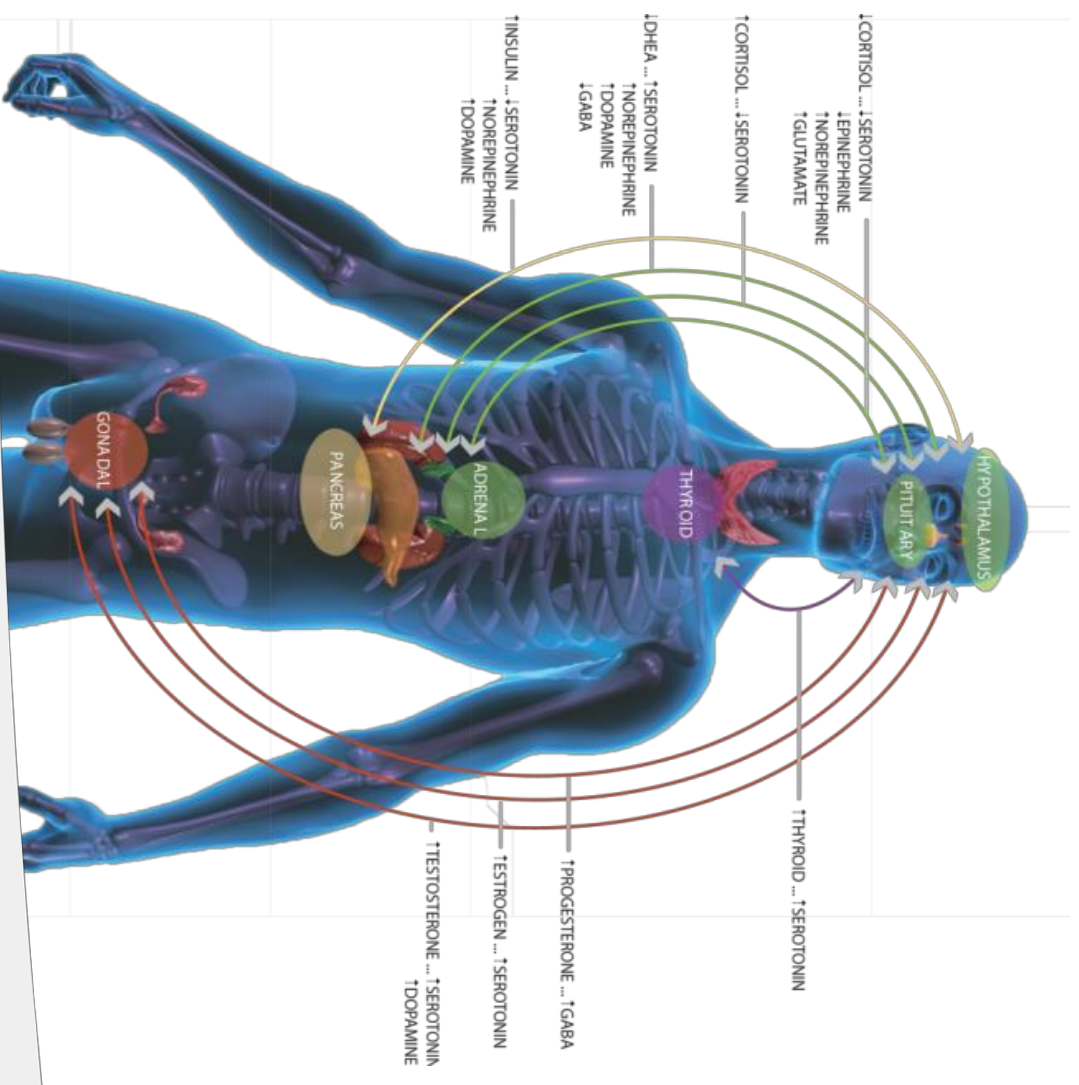


NeuroWellness Program™
Evidence-Based

Health in Balance

Path to Optimal Wellness

- Neuroendocrine health is key to quality of life.
- Clinical complaints begin to manifest when imbalances are present.



Health in Balance

Neuronal Pathways

- **Optimal function requirements**
 - **Balanced neurotransmitter release and reuptake** in the synapse
 - **Balanced HPA/T hormonal state**
 - **Neurotransmitter release** must be adequate and appropriate or intercellular communication cannot continue
- **Imbalance of the Neuro-immuno-endocrine communication system can lead to many pro-inflammatory degenerative diseases**

Health in Balance

Neurotransmitter Balance

- Optimal neuroendocrine health requires balance between **inhibitory and excitatory neurotransmitters**.
 - Inhibitory neurotransmission controls excitability and allows for calm, relaxation and sleep
 - Excitatory neurotransmission is essential for energy, focus and motivation
 - Inhibitory and excitatory neurotransmitters interact with adrenal and sex hormones

Calming Effect

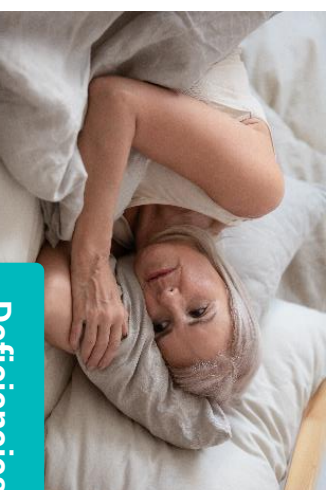
Inhibitory Neurotransmitters

- GABA
- Serotonin
- Can function as a *modulator* of other neurotransmitters
- Depletion symptoms are common in at **least 70% of patients** seen in the clinical setting
- Dopamine (both)



Excesses

- Sedation
- Poor impulse control
- Over inhibition leading to poor memory & cognition



Deficiencies

- Anxiousness
- Sleep difficulties
- Poor focus
- Low mood

Neurotransmitter Classification

Excitatory Neurotransmitters

- Dopamine (both)
- Norepinephrine
- Epinephrine
- Glutamate
- PEA



Excesses

- Anxiousness
- Sleep difficulties
- Poor focus
- Low mood
- Immune activity



Deficiencies

- Fatigue
- Burn out
- Uncontrolled urges

Neuroendocrine Testing

Measuring and Applying Neuroendocrine Results to
Clinical Situations

Path to Optimal Wellness

NeuroWellness Program™ Approach



Neuroendocrine Testing

- Lays out the most direct path to optimal health



Personalized Analysis

- The CARE package provides information connecting patient results to clinical concerns



Targeted Nutritional Therapy™

- Formulas provide only what is needed to address patient-specific imbalances

Neurotransmitters

Neurotransmitter Testing as a Clinical Tool

White Paper - Validity of Urinary Neurotransmitter Testing with Clinical Applications for the NeuroWellness Program™

22-page document with 117 references from the medical literature



Biomarkers Assessed

Urinary Neurotransmitters

- Serotonin
- GABA
- Epinephrine
- Norepinephrine
- Dopamine
- Glutamate
- PEA

Salivary Adrenal Hormones

- Cortisol
- DHEA-S

Salivary Sex Hormones

- Testosterone
- Progesterone
- Estrone (E1)
- Estradiol (E2)
- Estrone (E3)

NeuroWellness Program NeuroLab Sample Report

HPA-G Complete Profile (1)

NeuroLab
A Division of Sanesco International

Ordering Healthcare Provider
John Smith, MD
1200 W. Lurie
San Diego, CA 92103
USA

Date Collected
12/29/2019 8:01 AM PST
Sex Hormone Reference Range
Fast (Menopausal + HRT)
(Pre-Menstrual Cycle)

Date Received
01/01/2019

Report Final
01/29/2019

Report ID: 41149
Gender: F
Age: 63

Biomarker	Current Value	Optimal/Reference Range Guide
Serotonin	35.2 L	Optimal Range 125 - 260 <small>Reference Range 100 - 350</small>
GABA	299.0 L	Optimal Range 600 - 1100 <small>Reference Range 150 - 250</small>
Dopamine	202.8 L	Optimal Range 250 - 400 <small>Reference Range 100 - 350</small>
Norepinephrine	65.3 H	Optimal Range 30 - 50 <small>Reference Range 15 - 25</small>
Epinephrine	12.0	Optimal Range 10 - 15 <small>Reference Range 5 - 20</small>
Glutamate	14.1 H	Optimal Range 5 - 10 <small>Reference Range 2 - 12</small>
PEA	4.0	<small>Reference Range 1.0 - 2.0</small>
Norepi/Epi Ratio	5.4	< 13
Creatinine	100.0	No Range Available

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2114th Street, Aliso Viejo, CA 92656
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NeuroWellness Program NeuroLab Sample Report

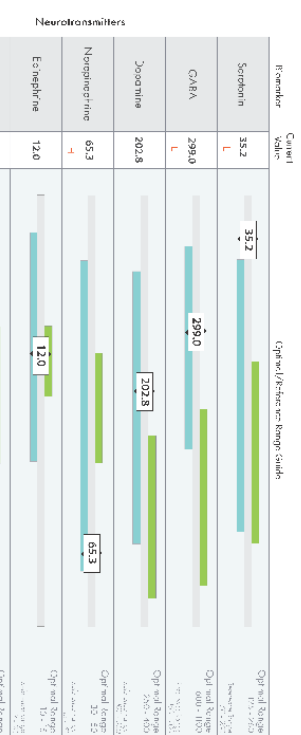
HPA-G Complete Profile (1)

NeuroLab
A Division of Sansero International

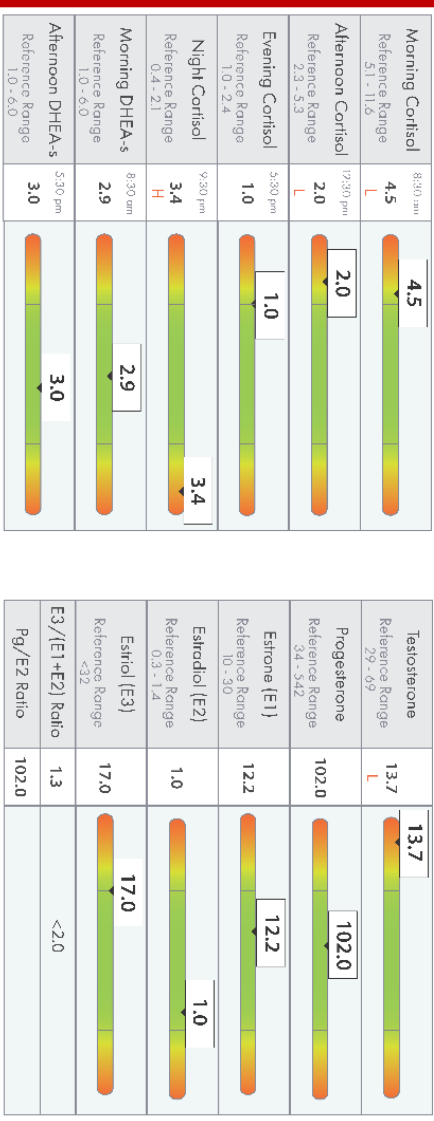
Referring Healthcare Provider
John Smith, MD
1 Decker Lane
San Diego, CA 92160
USA

Date Collected: 7/27/2018
Date Received: 8/1/2018
See: Hormone Reference Range
Ref: Metabolic - HRT
(Hormone Only)

Report Final: 8/1/2018
Patient: **Karla Doe**
Report ID: 8312
Gender: F
Age: 63



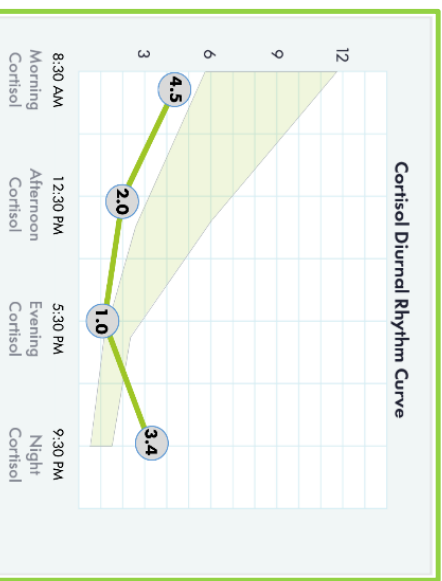
Adrenal Hormones Value



Sex Hormones Value



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Case Study

Clinical Presentation



- **CC:** 36 yo BF c/o fatigue, low mood, anxiousness, panic attacks, insomnia, “brain fog”, “cold intolerance”, hair loss, IBS, PMS, heavy, long menses. Wt gain 30 lbs in past 10 yrs
- **PMH:** G₂P₂ Hosp: none Surg: FBD w/ 1 breast bx of a sm nodule – B9
- **Illness:** Hx of pp low mood worse with second child
- **FH:** mom 58 low mood, dad 62 CAD, HTN, 1 sis 38 bipolar low mood, hypothyroid. Hx breast Ca, uterine Ca. Thyroid common on maternal side. CAD on paternal
- **SH:** Divorced, Nonsmoker, ETOH 1-2 week. Caffeine + 3 cups per day. No regular exercise. Diet hi carb, hi fat, low protein
- **Med:** Sertraline 75 mg/day x10 years

Case Study

Clinical Presentation



- OTC: MVI, Cal/Mag, Valerian for sleep
- Allergies: PCN – rash
- ROS: Long hx of low mood and PMS for at least 15 years, panic attacks began after birth of first child. Hypoglycemia. SAD. PMS. Mastodynia. Low libido. Exhaustion
- PE: BP 98/60, p82, h5'4", w157, Body Fat: 36%, BMI: 26.9
Cold hands and feet, pale coloring, thin hair and splitting nails.
Cystic breasts. Anxious demeanor

Case Study

Serum Hormone Results



Hormone	Result	Range
Luteal Phase (day 18-21 of cycle)		
TSH	normal range (ultra sensitive) 4.6 mIU/L	(*normal range* 0.34-5.6 mIU/L, optimal range < 2.0mIU/L)
Free T3	1.9	(normal range: 2.4 - 6.8pg / ml)
Free T4	0.7 ng/dl	(normal range: 0.7-1.6 ng/dl)
Thyroid	auto antibodies present	
Estradiol	high	normal at 1.9 pg/ml.
Estrone	high at 35	33.8 pg/ml.
Progesterone	33.8 pg/ml.	
Testosterone	20.6 pg/ml	(Range 26 - 98)
Free Testosterone	0.6	(Range 1 - 3) (serum)
DHEA-S	2.5 ug/ml @ 8 a.m., and 0.7 @ 4 pm	(Mean Range: 1.0 - 6.0 ♀ age 20-30)
SHBG	Elevated 128 nmol/L	(Range: 30 - 85)

Case Study

Baseline Salivary Hormones

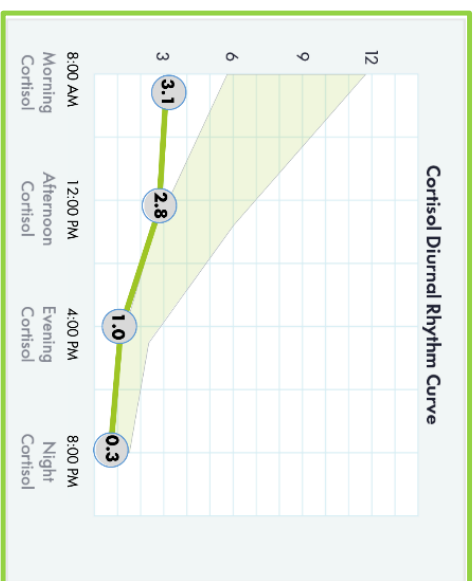
Hormones

Measure salivary cortisol

• 8 am, 12 pm, 4 pm, 8 pm, 8 pm

Measure salivary DHEA-S

• 8 am and 4 pm



Neurotransmitter

Serotonin

- AKA 5-HT or 5-hydroxytryptamine
- 1-2% in CNS
- 95% in gut enteric nervous system
- 2-3% in platelets

- **Inhibitory neurotransmitter**

- **Neuromodulator**

- Affects glutamate excitability over diverse regions of CNS
- Acts by stimulating its own receptors on GABA neurons, prompting GABA to perform its inhibitory function
- Acts to inhibit the release of the catecholamines ("CATS"): dopamine, norepinephrine, epinephrine

Low Serotonin

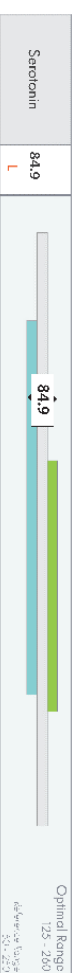
- Decreased mood
- Anxiousness
- Carbohydrate cravings
- Poor sleep
- Anger/Rage
- Discomfort
- Headaches
- Constipation
- PMS/Hot flashes

Case Study

Thyroid Discussion



- Common clinical presentation of a 36-year-old woman w/ a hx of long-standing anxious low mood, Hashimoto's thyroid disorder with a low thyroid/adrenal state and relative estrogen dominance.
- Low T3, poor T4 to T3 conversion, blunted TSH response possibly 2° to low serotonin and an imbalanced HPAT axis.



Case Study

Estrogen Dominance Discussion



Proliferative Estrogen Dominance made worse by:

- Low T3/T4 Thyroid
- Low Luteal Phase Progesterone
- Low 2:16 ratio of Estrogen Metabolism
- Low Adrenal DHEA-S/Cortisol

CC are exhaustion, PMS, weight gain & disruptive circlothymic mood disorder; deep low mood alternating w/ panic attacks, worse the week before menses and in the dark days of winter

Morning Cortisol Reference Range 5.1 - 11.6	8:00 am 6.7	3.1 L	
Afternoon Cortisol Reference Range 2.3 - 5.3	12:00 pm 3.0	2.8	
Evening Cortisol Reference Range 1.0 - 2.4	4:00 pm 1.4	1	
Night Cortisol Reference Range 0.4 - 2.1	8:00 pm 1.0	0.3 L	
Morning DHEA-s Reference Range 1.0 - 6.0	8:00 am 3.8	2.5	
Afternoon DHEA-s Reference Range 1.0 - 6.0	4:00 pm 2.9	0.7 L	

Adrenal Fatigue & NT Balance

- "Adrenal Fatigue", with cortisol and DHEA depletion, can lead to:
 - Low epinephrine level
 - Elevated Norepi/Epi ratio
- Adequate *cortisol* is needed for the precursor NE to be converted to epinephrine (1)



Your husband is suffering from a very severe stress disorder. If you don't do the following he will surely die. Each morning fix him a healthy breakfast. Be pleasant at all times. For lunch make him a nutritious meal. For dinner prepare an especially nice meal. No chores. No nagging. Oh yes, and make love several times a week.



Do this for the next year and he'll regain his health completely!



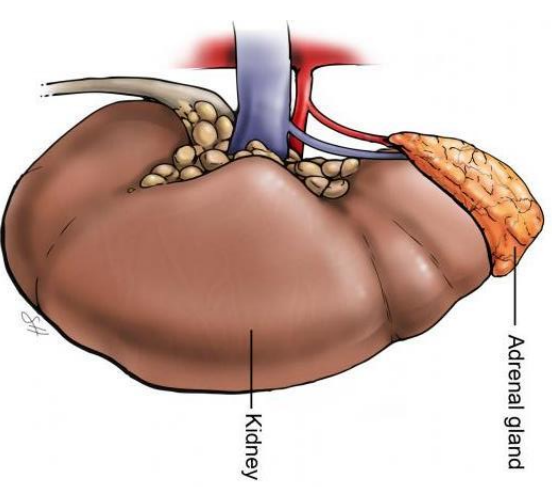
What did the doctor say?

You're going to die!

Neuroadrenal

Epinephrine

- Functions both as a neurotransmitter and a hormone, but clinically primarily acts as a hormone
- Major peripheral Adrenal Hormone mediating **Acute Stress Response**
- CNS Epi (as NT) functions not well studied
- Works more on periphery
 - Blood pressure control, HR
 - Increased energy
 - Methamphetamine blockage of Epi re-uptake – burn out

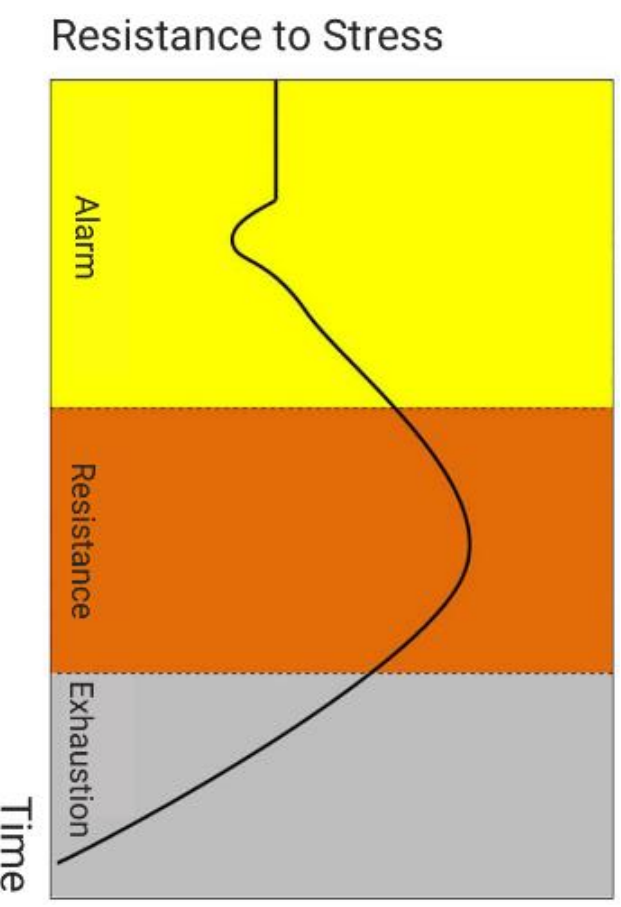


Epinephrine, the Hormone

- Profound effect on metabolism: catabolic hormone breaking down body stores of fuel for perceived stress
- Upregulates every system that can contribute to “fight or flight” responses:
 - Increases heart rate, metabolic rate, glucagon, sodium retention and elevates BP
 - Dilates bronchii, pupils, small arteries in muscles
 - Raises blood glucose via gluconeogenesis and glycogenolysis (1)
- Chronic stress-mediated over-activation of Epi can lead to insulin resistance (2)

Phases of Stress Response

- Phase I: Alarm reaction
 - Hi Epi
 - Hi Cortisol
- Phase II: Resistance
 - Hi Cortisol
 - Low DHEA
 - Epi variable
- Phase III: Exhaustion
 - Depletion of Cortisol
 - Depletion of Epi
 - Depletion of DHEA



Many patients are in the resistance/exhaustion phase



Case Study

Norepi/Epi Ratio Discussion

- **Norepi / Epi ratio elevated:**
 - Biochemically, the synthesis of epinephrine from norepinephrine is dependent on adequate cortisol and SAME
 - "Adrenal Fatigue"** with low DHEA/cortisol
 - Insulin resistance with blood sugar instability, RHG (reactive hypoglycemia), inflammatory disorders
 - Clinically, this can be caused by and further perpetuate Sympathetic Autonomic Nervous System over-activation leading to "Fight or Flight" reactions




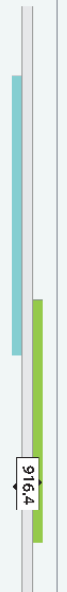

Norepi/Epi Ratio	27.9 H	< 13
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Case Study

Neurotransmitter Discussion

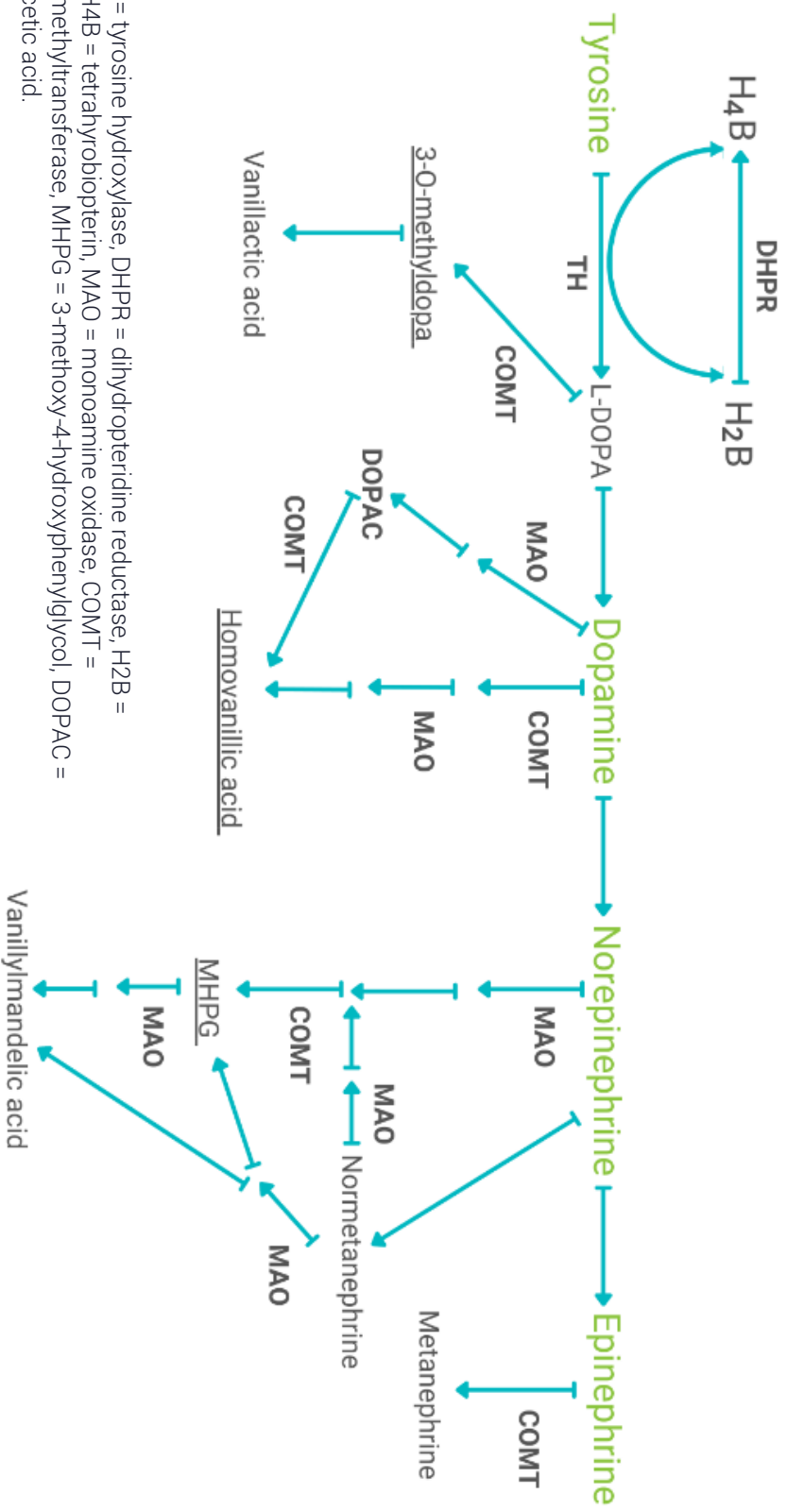
- Low Serotonin – even though patient is on sertraline an SSRI
- Serotonin depletion/Norepinephrine excess
- Results in patient's presentation of anxiousness, fear, and poor sleep
- Serotonin is responsible for maintaining homeostasis among the excitatory catecholamines (i.e. Norepinephrine)
- Serotonin's depletion leads to a strong tendency towards Sympathetic Autonomic Nervous System over activation under Norepinephrine stimulation



Serotonin	84.9 L		Optimal Range 175 - 260 Neurotransmitter 175-260
GABA	916.4		Optimal Range 600 - 1100 Neurotransmitter 600-1100
Dopamine	110.2 L		Optimal Range 250 - 400 Neurotransmitter 250-400

Neurotransmitters

Catecholamine Pathways - "The CATS"



Abbreviations: TH = tyrosine hydroxylase, DHPR = dihydropteridine reductase, H2B = dihydrobiopterin, H4B = tetrahydrobiopterin, MAO = monoamine oxidase, COMT = catecholamine-O-methyltransferase, MHPG = 3-methoxy-4-hydroxyphenylglycol, DOPAC = dihydroxyphenylacetic acid.

Neurotransmitter **Norepinephrine**

- Peripheral Sympathetic Nervous System norepinephrine mediates:
 - *Perception* of “fight or flight” stress response
 - Norepinephrine firing is kept under control by GABA (Serotonin) inhibition
- CNS norepinephrine mediates:
 - Mood regulation, sleep dysregulation, drive, ambition, learning/memory, alertness, arousal and focus



Neurotransmitter

Serotonin/Norepinephrine

- There is often an **inverse relationship** between excitatory neurotransmitters & inhibitory neurotransmitters
- When inhibitory neurotransmitters are low, norepinephrine or glutamate may be **over-expressed** →
 - "Fight or flight" responses
 - Elevated blood pressure
 - Anxiousness and fear



Neurotransmitter

Glutamate

- Primary excitatory neurotransmitter
- Synthesized from glutamine or glucose
- Glutamate receptors (e.g., NMDA) subject to excitotoxicity
 - MSG, Aspartame
 - Subject to dietary intake

Neurotransmitter

Glutamate

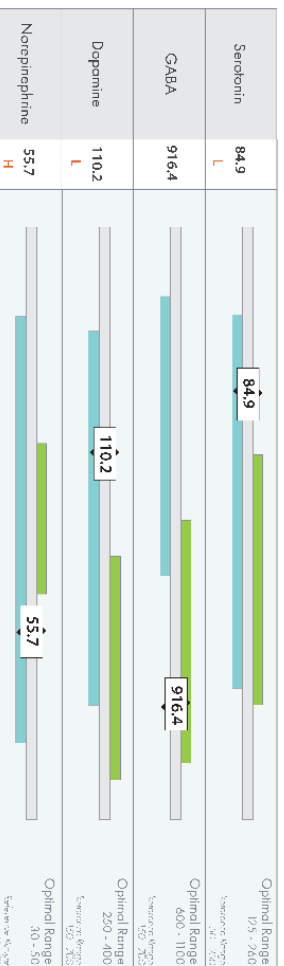
- Excitotoxicity = Neuron Damage/Death
- MSG, aspartame play a role in excess glutamate excitotoxicity
“Sodium” on food labels
- Glutamate also seems **necessary for TSH to rise** and causes a rise in thyroid hormones (1)
- Glutamate regulates neurogenesis
 - Synaptogenesis and neuron survival in the developing and adult mammalian nervous system (2)

1. Aizawa S, et al. (2012). J Endocrinol. Mar;212(3):383-94.
2. Mattson MP. (2008). Ann N Y Acad Sci. November; 1144: 97–112.

Case Study

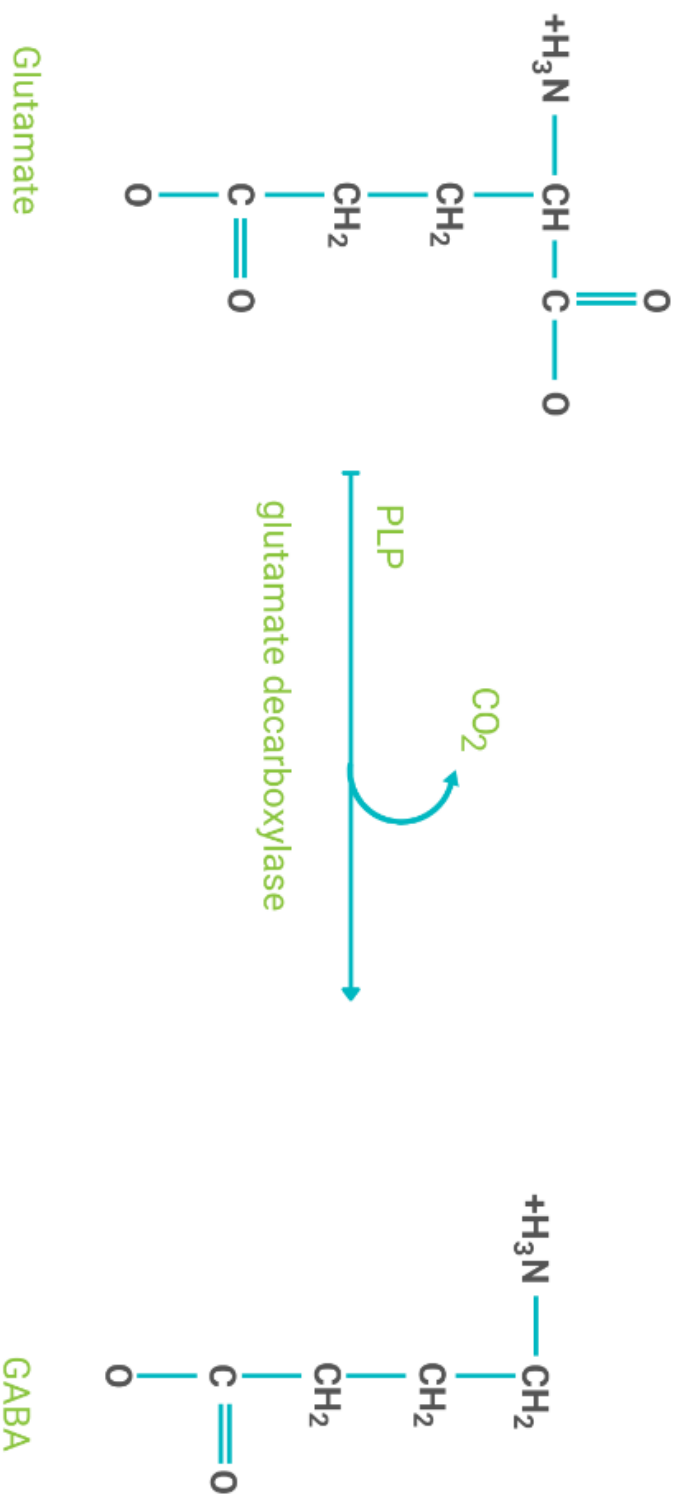
GABA Discussion

- **GABA elevated:**
 - Elevation reflects excess GABA production and turnover to compensate for absence of adequate inhibitory serotonin
 - GABA itself then tries to **balance the unopposed release** of norepinephrine
 - Clinically, high urinary GABA may be a sign of **depleted CNS GABA** over time, representing the need for GABA support



Neurotransmitters

GABA Pathway



Importance of glutamate apart from excitation: it is converted to the physiologically active gamma-aminobutyric acid (GABA), the major CNS inhibitory NT

Neurotransmitters

GABA

- Too much excitation without adequate GABA inhibition can lead to:
 - Poor sleep
 - Restlessness
 - Irritability
 - Anxiousness
 - Fear
 - Seizures
- GABA induces **relaxation, calmness & aids sleep**
- Theanine, Lactium (milk peptides), taurine, inositol, and oral bio-identical progesterone can act as nutraceutical GABA agonists



Neurotransmitter & Hormone Interactions

Progesterone & GABA

- Allopregnanolone, an active metabolite of 1^o oral Progesterone
- Allopregnanolone is one of the **most potent known modulators of GABA_A receptors (1)**

Dopamine



Quizzo!!

Norepinephrine or dopamine may be over-expressed resulting in “fight or flight”, anxiousness, panic, or delusional thinking when:

- a) Serotonin is low
- b) GABA is low
- c) Glutamate is low
- d) There is a full moon
- e) a & b

Neurotransmitters

Dopamine Inhibition

- Serotonin through its action on the serotonin 2C receptor **inhibits dopamine release**, contributing to lack of responsiveness to SSRIs in some patients (1)
- SSRIs shown to increase the dopamine transporter in vivo, thereby **reducing dopamine function (2)**

1. Visser AK, et al. (2015). *Neurochem Int.* Feb;81:10-5.
2. Podurgiel SJ, et al. (2015). *Neuropsychopharmacology.* Mar 11.

- SSRIs are associated with a risk of clinically significant loss of sexual desire in at least 30-50% of those that take them.
- Reduced mesolimbic dopaminergic activity as a result of inhibitory serotonergic midbrain raphe nuclei projections is one possible cause.
- Animal studies show that increased serotonergic tone predicts ejaculatory latency by acting as an inhibitor at the hypothalamus level. In contrast, noradrenergic tone enhances ejaculation.
- Prabhakar D, Balon R. How do SSRIs cause sexual dysfunction? Current Psychiatry (2010): Vol. 9, No. 12. p. 30-34.

be fundamental to SSRI-associated sexual dysfunction.

Not just serotonin

Although SSRIs are relatively selective for the serotonergic system, they affect other neurotransmitter systems

Neuroendocrine Interactions

The Impact on Clinical Presentation

The Seven Dwarves of Menopause

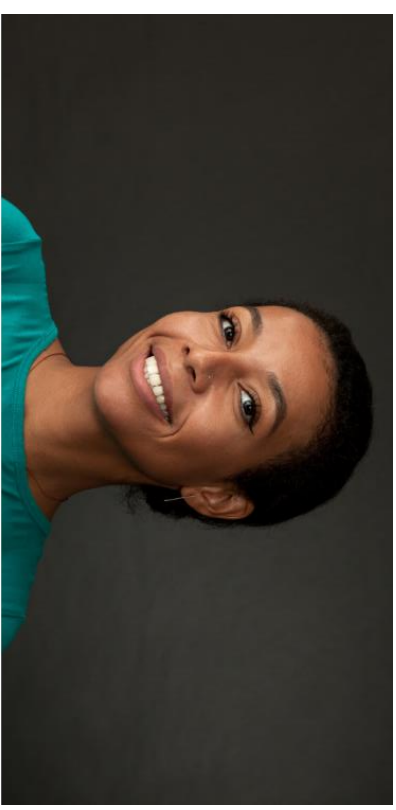


Itchy, Bitchy, Sweaty, Sleepy, Bloating, Forgetful & Psycho

Neuroendocrine Interactions

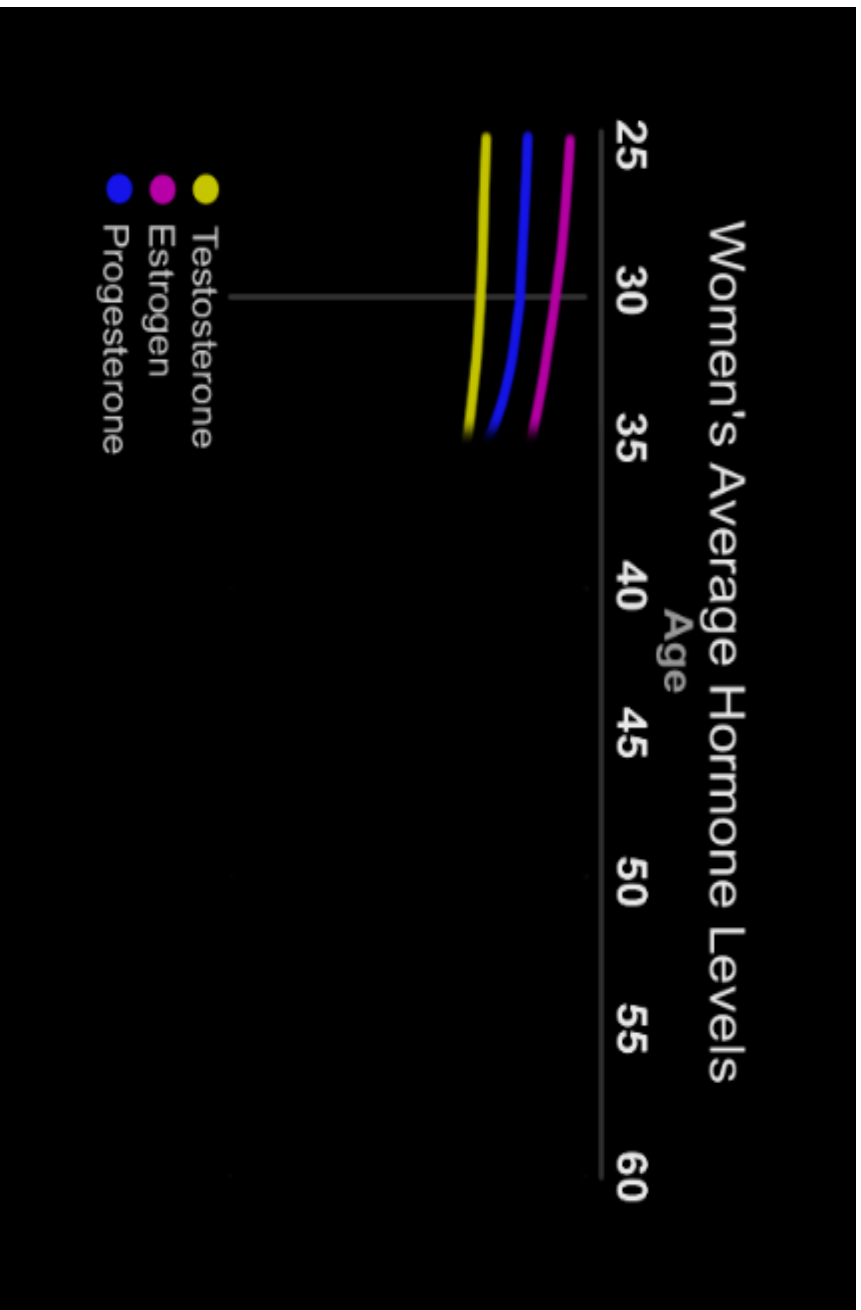
Transitional Years

- Age 35 years+ – anovulation - ↓ progesterone
 - Anxious, loosing sleep - ↓ GABA
- Age 45 years+ - ↓ estrogen - ↓ serotonin
 - Fatigue
 - Insomnia
 - Migraines
 - Hot flashes/vasomotor instability
 - Decreased brain function/memory issues
 - Low mood/anxiousness/Emotional volatility



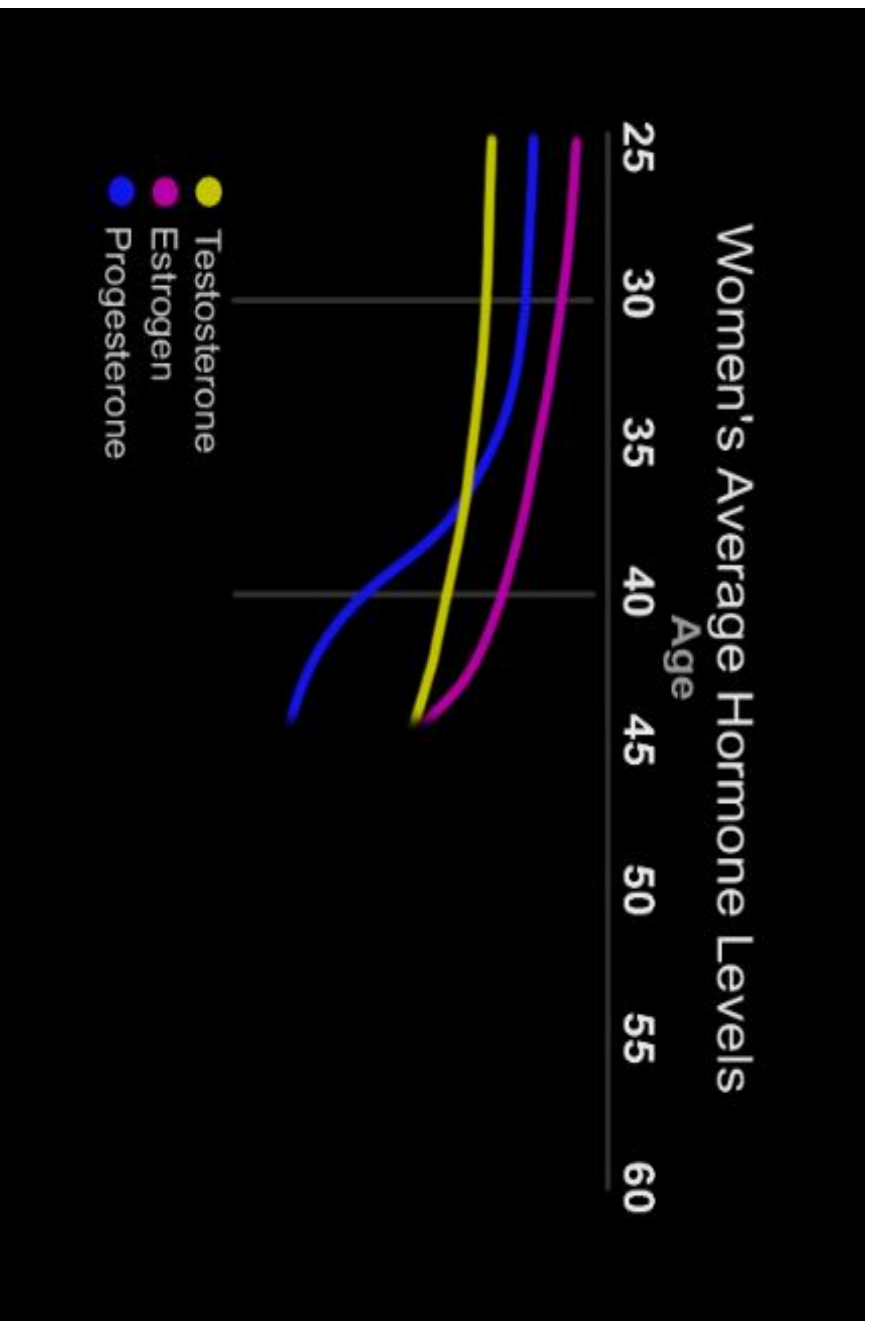
Neuroendocrine Interactions

Women's Average Hormone Levels

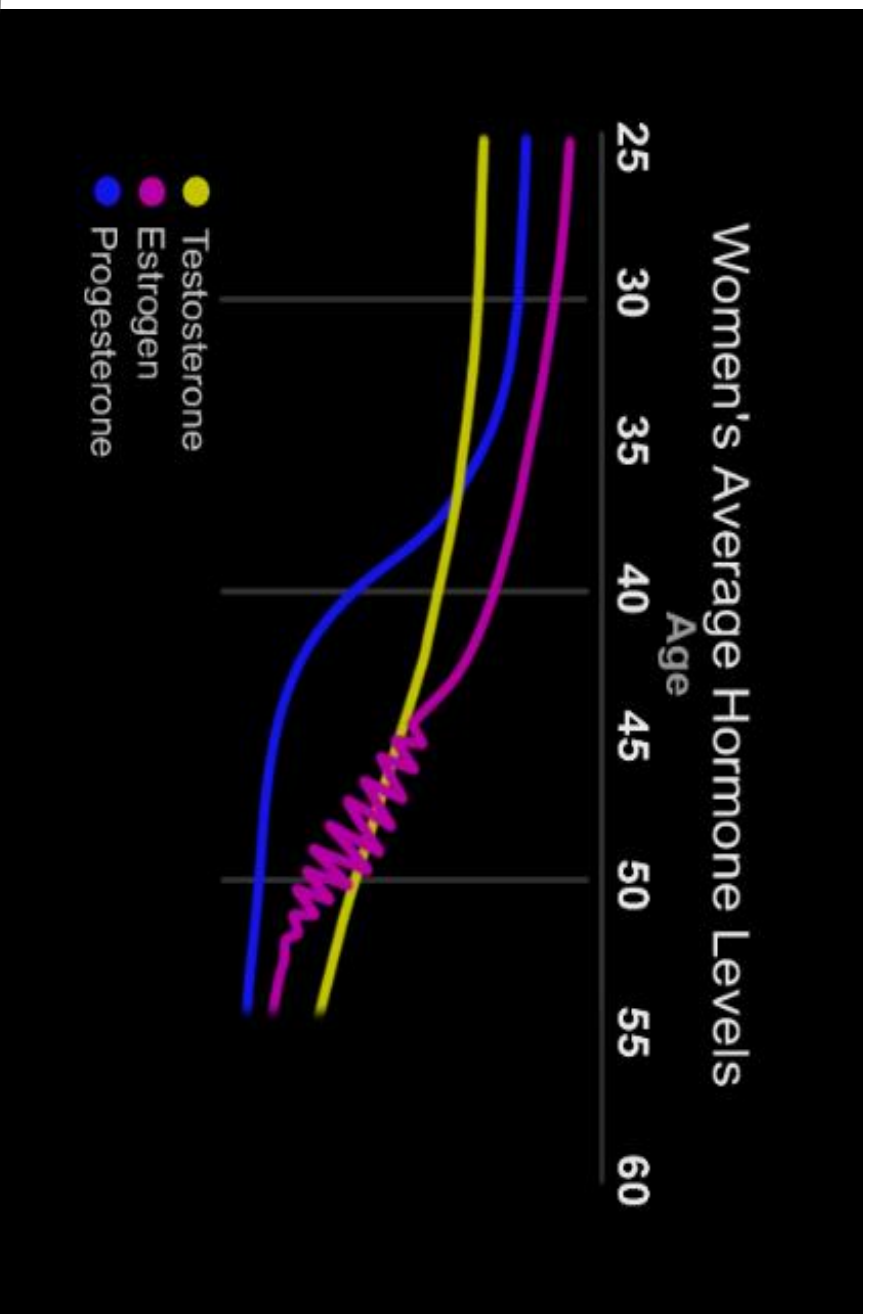


Neuroendocrine Interactions

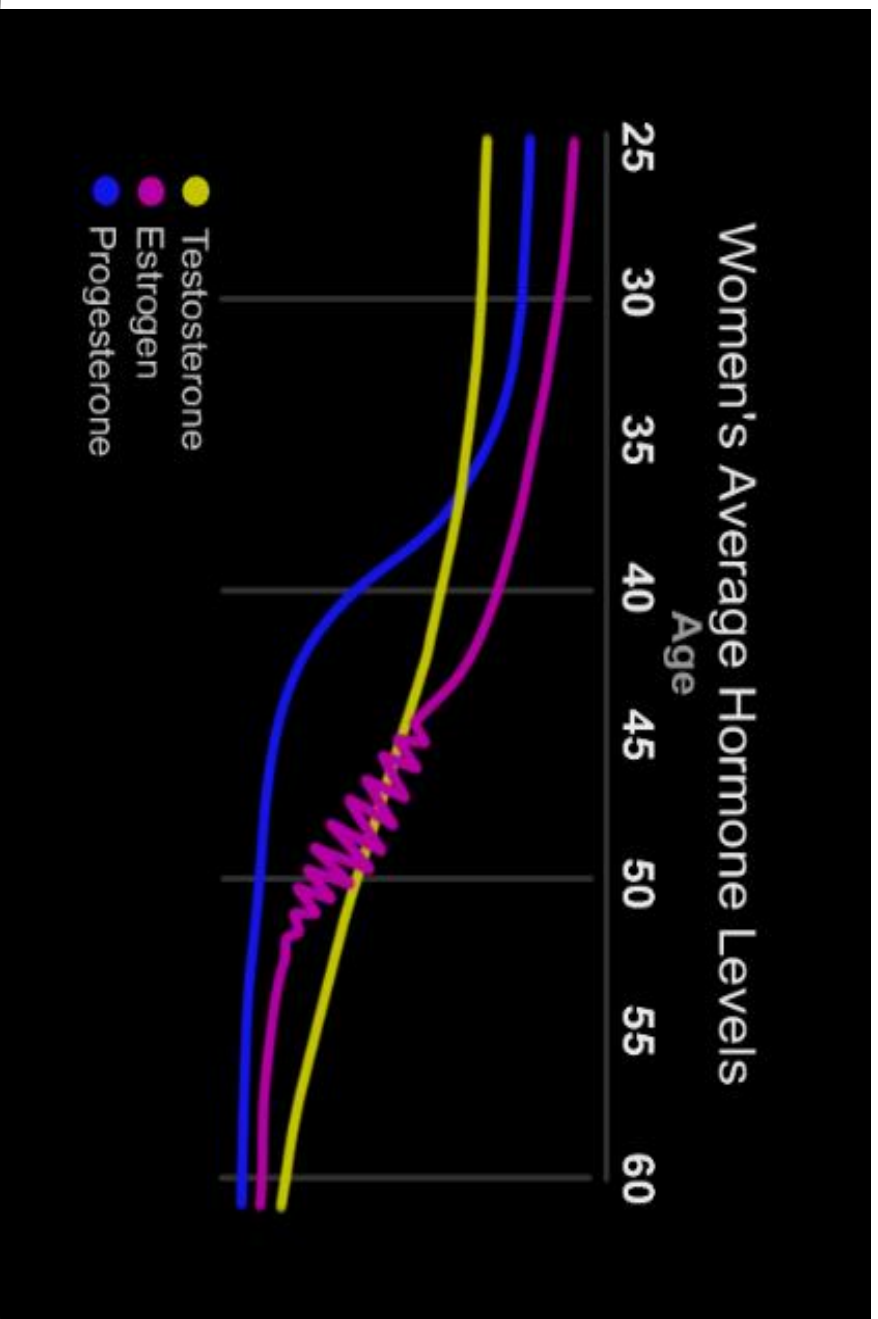
Women's Average Hormone Levels



Women's Average Hormone Levels



Women's Average Hormone Levels



Neuroendocrine Interactions

Hormone Effects on Neurotransmitters

- Estrogen: serotonin agonist, dopamine modulator
- Progesterone: GABA agonist
- Testosterone: serotonin agonist, dopamine agonist
- DHEA: dopamine, NE, serotonin agonist, GABA antagonist
Neuro-protective, ↑↑ Neuronal plasticity
- Thyroid: serotonin agonist
- Cortisol excess: blocks serotonin and tryptophan metabolism into serotonin; use 5-HTP to bypass
- Cortisol deficiency: ↓↓ serotonin, epinephrin, ↑↑ norepinephrine, glutamate
- Insulin excess (Insulin Resistance): ↓↓ serotonin, ↑↑ NE, dopamine

Neurotransmitter Effects on Hormones

- Serotonin: ↑↓ thyroid function
Necessary to ↑↓ TSH appropriately for feedback loop stimulation of FT3 and FT4
- Adrenal support: ↑↓ cortisol appropriately
- GABA: Inhibits thyroid function
- Dopamine: ↓ Prolactin, ↑ Growth Hormone
- NE excess: Acute: ↑ Cortisol
Chronic: ↓ Cortisol
- Epinephrine excess: Insulin Resistance - ↓ Insulin

Case Study

Estrogen/Thyroid/Serotonin Discussion

Estrogen Dominance/Thyroid Function:

Estrogen can dominate over thyroid by 2 mechanisms

- Elaborating TBG (Thyroid Binding Globulin) which binds (inactivates) free thyroid hormone (1)
- Competitive inhibition of the thyroid receptor: By binding the thyroid receptor, estrogen blocks the binding of thyroid hormone to its own receptor

Both actions → lower thyroid function

Since thyroid acts as a serotonin agonist, **estrogen dominance can result in lower serotonin function**



Serotonin	84.9
	L

Case Study

Estrogen/Progesterone/GABA Discussion

Estrogen Dominance & Progesterone:

- Anovulatory menstrual cycles are common for women after age 35 in industrialized countries
- Without ovulation, **no progesterone is produced** in the luteal phase of the menstrual cycle
- Thus, estrogen is produced **unopposed** all month-long
- Since progesterone is a GABA agonist, anovulatory menstrual cycles may result in **lowered GABA function**

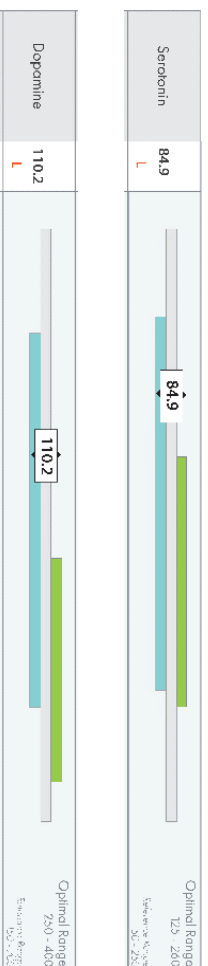


Case Study

Estrogen/Testosterone/Serotonin/Dopamine Discussion

Estrogen Dominance & Testosterone

- Mechanism: elaboration of SHBG (Sex Hormone Binding Globulin)
- SHBG binds **free testosterone**, rendering it unable to bind its own receptor and therefore inactive
- Lab: Total testosterone - low / Free testosterone - low
- Testosterone can act as a **serotonin and dopamine agonist**. Therefore, this may result in lowered serotonin and disordered dopamine function





Case Study

Thyroid/Serotonin Discussion

Thyroid imbalance:

- Hashimoto's Thyroid disorder is the most common cause of hypothyroidism, found in a 50:1 ratio of women to men
- T3 and T4 circulate \neq 95% bound to plasma proteins (TBG, Albumin, Pre-albumin)
- All thyroid hormones are optimally measured in their free unbound state (Free T3, Free T4)
- Therefore, reliance on TSH alone, without free T3 and free T4 measurements, is **inadequate to assess true thyroid function** – particularly in the context of low serotonin states



Case Study

Adrenal Discussion

Adrenal imbalance:

- Cortisol and DHEA have an **inverse relationship in acute stress** with DHEA-S levels dropping as cortisol levels rise
- The two-point salivary, Adrenal Index (AI), measurement of am and pm DHEA-S allows the assessment of bio-chemically individual diurnal patterns and levels:
- What time of day
- How much
- How often to best replace DHEA for any patient



Morning Cortisol Reference Range 5.1 - 11.6	8:00 am 3.1 L	3.1	
Afternoon Cortisol Reference Range 2.3 - 5.3	12:00 pm 2.8	2.8	
Evening Cortisol Reference Range 1.0 - 2.4	4:00 pm 1.0	1.0	
Night Cortisol Reference Range 0.4 - 2.1	8:00 pm 0.3 L	0.3	
Morning DHEA-s Reference Range 1.0 - 6.0	8:00 am 2.5	2.5	
Afternoon DHEA-s Reference Range 1.0 - 6.0	4:00 pm 0.7	0.7	

Excess Cortisol & Serotonin

- Excess cortisol has an inhibitory effect on serotonin function via **at least 4 known mechanisms**:
 1. Corticosterone treatment was found to induce a ... functional desensitization of somatodendritic 5-HT(1A) autoreceptors(1)
 2. Corticosterone treatment significantly decreased the number of 5-HT1A receptor sites(2)
 3. "Cortisol at the nM-microM concentration range induces a substantial **increase in serotonin uptake** both in vitro ...and in vivo, ... owing to promotion of synthesis of the serotonin transporter" (3)
 4. Tryptophan metabolism is shunted to kynurenine pathway by elevated cortisol(4)

NOTE: 5-HTP bypasses the TO enzyme and thus can raise serotonin even in the face of excess cortisol

1. McAllister-Williams RH, et al. (2007). J Psychopharmacol. Nov;21(9):826-32.
2. Crayton JW, et al. (1996). Brain Res. Jul 29;728(2):260-2.
3. Tafet GE, et al. (2001). Cogn Affect Behav Neurosci. 1(1):96-104.
4. El Bakly WM, Hasanin AH. (2014). Korean J Physiol Pharmacol. Jun;18(3):233-9.

Neuroendocrine Interactions

Low Cortisol & Serotonin

“In the amygdala, if endogenous cortisol is removed, 5-HT no longer has an inhibitory effect on glutamatergic activity, suggesting that this hormone (*cortisol*) plays a key role in maintaining serotonergic-mediated modulation.”

Stutzmann GE, McEwen BS, LeDoux JE. *J Neurosci*. 1998. Nov. 15;18(22):9529-38.

Case Study

Neurotransmitter-Hormone Summary

36-year-old woman

w/: Anxious, low mood, Panic Attacks, PMS, RHG, SAD, Mastodynia, Exhaustion, 30 lb. weight gain & ↓ Libido

Hormonal Concerns:

- Hashimoto's Thyroid disorder with low T3
- Adrenal Fatigue with low DHEA/Cortisol
- Estrogen Dominance w/ ↓ P4, Testosterone, T3

Neurotransmitter Concerns:

- ↑↑ Norepinephrine mediated Sympathetic ANS dominance over ↓↓ inhibitory serotonin w/ ↑↑ compensatory GABA response
- ↓↓ Dopamine (modulator) = Low "salience"
- ↑↑ Norepi/Epi ratio; needs SAMe & Cortisol



Case Study

Summary

- This case exemplifies the importance of the **timing and sequence** of hormonal and TNT (Targeted Nutritional Therapy) to restore the balance of the Neuro-Endocrine Communication System
- As always, restoration of the Neuro-Inhibitory axis of the CNS by balancing both Serotonin and GABA is the **first** important clinical step
- Without optimal inhibitory function, the much-needed replacement of tyrosine, a precursor for catecholamine & thyroid support, DHEA, and/or cortisol, T3 / T4 Thyroid hormone may further exacerbate the patient's elevated norepinephrine mediated "fight or flight" responses, leading to worsening anxiousness and panic attacks

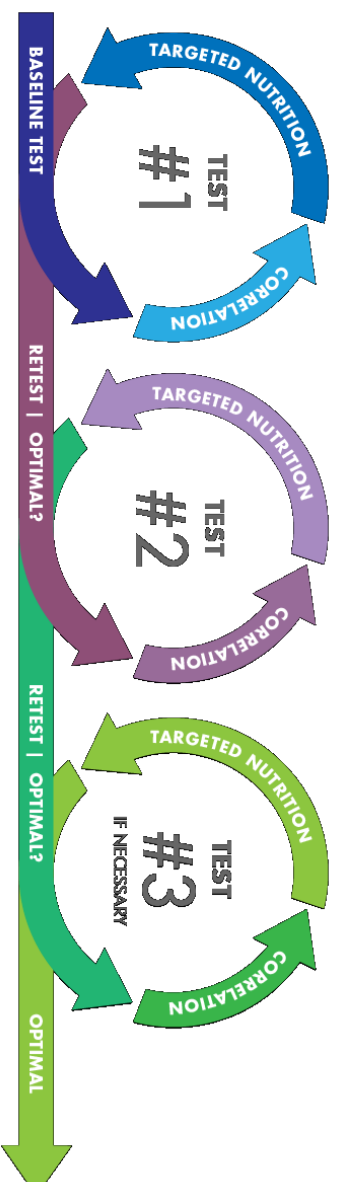


Overview

Steps for Promoting Balance

1. Restore inhibitory neurotransmitter levels (serotonin and GABA)
2. During or after inhibitory neurotransmitter balance restoration
 1. Support catecholamines
 2. Support adrenal hormones
 3. Support with thyroid replacement when appropriate
 4. Support sex hormones
3. Maintain

NeuroWellness Program Process



NeuroWellness Program

Retest

HPA-G Complete (Retest Report)



Referring Healthcare Provider
John Smith, MD
 Doctor's Office
 San Diego, CA 92108
 USA

Date Collected 01/29/2022
 Date Received 02/02/2022
 Serotonine Reference Range 57-113 female

Report Final 02/22/2022

Patient
Jane Doe
 Report ID: # 8198
 Gender: F
 Age: 35

Neurotransmitter	Value	Reference Range	Optimal Range
Serotonin	311.7 H	57 - 113	129 - 260
GABA	634	600 - 1100	600 - 1100
Dopamine	252.8 L	300 - 350	250 - 400
Norepinephrine	36.1 H	30 - 50	30 - 50
Epinephrine	5.2 L	5 - 15	10 - 15
Glutamate	7.5 H	5 - 10	5 - 10
PEA	5.5	1.5 - 2.5	1.5 - 2.5
Norepi./Epi Ratio	6.9 H	< 13	< 13
Creatinine	100	No Range Available	No Range Available



NeuroLab 110 02116 P 1481100017 7176701 DINA Address: 1830 N. 106th Street, #100, San Diego, CA 92121

NeuroWellness Program Retest

HPA-G Complete (Retest Report)

NeuroLab
A Division of Sansero International

Referring Healthcare Provider: **John Smith, MD**
 Date Collected: **01/29/2022**
 Date Received: **02/01/2022**
 Report Final: **02/21/2022**
 Sex: **Female**
 Age: **55**
 Referring Facility: **Cycling Female**
 Report ID: **1910**
 Gender: **F**
 Age: **55**

Biometric	Current Profile Value	Reference Range Guide	Optimal Reference Range Guide
Serotonin	3117 H	64.0 L	120-254 3117
CANX	634 H	918.4 L	219-5 634
Dopamine	252.8 L	1.0-2.0	12.5-24 322.8
Norepinephrine	36.1 H	33.7 L	12.5-24 36.1
Cortisol	5.2 L	2.0 L	12.5-24 5.2
Cholesterol	7.5 H	18.1 L	12.5-24 7.5
PEA	5.5 L	3.2 L	12.5-24 5.5

Neurotransmitters	Testosterone	Progesterone	Estrone (E1)	Estradiol (E2)	Estrone (E3)	E3/(E1+E2) Ratio	Pg/E2 Ratio
Morning Cortisol Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9
Afternoon Cortisol Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9
Evening Cortisol Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9
Night Cortisol Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9
Morning DHEA-s Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9
Afternoon DHEA-s Reference Range: 1.0-2.0 Reference Range: 2.3-3.3	32.9 L	70.4 L	27.6 H	1.5 L	21.2 L	0.7	46.9



1. All values are reported in units of the respective test. NeuroLab is a division of Sansero International, Inc. All tests are performed in a CLIA-certified laboratory. NeuroLab is a division of Sansero International, Inc. All tests are performed in a CLIA-certified laboratory. NeuroLab is a division of Sansero International, Inc. All tests are performed in a CLIA-certified laboratory.

CARE Package Add-On

Analysis and Intervention

Path to Optimal Wellness

NeuroWellness Program™ Approach



Neuroendocrine Testing

- Lays out the most direct path to optimal health



Personalized Analysis

- The CARE package provides information connecting patient results to clinical concerns



Targeted Nutritional Therapy™

- Formulas provide only what is needed to address patient-specific imbalances

Referring Healthcare Provider	Done Collected	Done Received	Report Final	Patient
John Smith, MD	06/18/2021	06/29/2021	06/18/2021	Mary Thompson
1 Doctor Lane San Diego, CA 92240 USA	See Homecare Reference Range Point Menopausal			Report ID: #349782 Gender: F Age: 58

The Neuro Wellness Program and Your Patient

The object of the Neuro Wellness Program is to help restore balance to the HPA axis. One of the consequences of the CSM model is to monitor neurotransmitter and adrenal hormone levels by relating the patient through the laboratory process. This is the most effective way to guide individual therapy. The patient's current laboratory values can be measured against reference skills, allowing for imbalances to be more objectively addressed. Targeted Nutritional Therapy™ can be adjusted as results are compared. With each visit, the aim is to move the patient closer to achieving HPA axis balance and an improved sense of well-being.

Patient has noted they have been diagnosed with one of the AUTO-IMMUNE DISEASES. Consider thorough functional medicine work up to include standard lab testing for auto-immune disease as well as testing for intestinal permeability and comprehensive stool analysis to assess the gut.

*The patient indicated medications that may be influencing results.

Since the last test, the patient has seen some concerns diminish completely (excessive appetite, seasonal allergies, night sweats, and nervousness) and a decrease in the severity of other concerns (low libido, decreased stamina, abdominal weight gain, depression with nervousness, poor sleep, and irritability). Overall, the patient is showing great improvements.

The patient's current anxiety, depression with nervousness, poor sleep, and irritability may be related to the current serotonin and GABA levels. Even though the serotonin and GABA levels have increased significantly since the last test, they remain suboptimal. The inhibitory neurotransmitter serotonin and GABA function together to promote calm, relaxation, and a sense of well-being. Therefore, consider continuing with serotonin and GABA support to help restore optimal inhibitory neurotransmitter function and potentially assist in further improving the patient's mood and sleep concerns.

The patient's current low libido and decreased stamina may be related to the current dopamine and epinephrine levels. These neurotransmitter levels have decreased due to the chronic inflammation support. Consider additional support for dopamine and epinephrine level maintenance. Consider implementing supplemental catecholamine support to help restore dopamine and epinephrine levels and potentially assist in further improving the patient's libido and energy concerns. The patient's cortisol hormone levels are now within range, likely indicating adequate adrenal function. The patient's supplemented adrenal support may be slowly tapered down with the guidance of their healthcare provider.

The patient's sex hormone levels are now within range. The healthy increase in the testosterone level may be due to the slight improvement in the DHEA levels. The estrogen ratio remains slightly low. This may be due to the balance between estrogen, estradiol, and estrone being low relative to estrone and estradiol. Estrone is considered the less potent of the other estrogens as it can antagonize some of the proliferative properties of estrogen and estradiol. By judiciously supporting healthy estrone levels (ie stress reduction), the estrogen ratio may potentially improve.

Re-testing is recommended in 10-12 weeks from starting the suggested therapeutic protocol to monitor the restoration process and make any necessary adjustments to the therapeutic protocol.

*NOTE: This service is reserved for practitioner use only. This report was written for you by Nathan Bridges. We strive to create the highest quality reports, and encourage our practitioners to contact our Clinical Support Specialists with any questions or concerns. We can also arrange for an interpretation of the patient's results, based on your schedule and availability. To reach the report writer directly, dial 866-670-5705.

Neurotransmitter Correlation

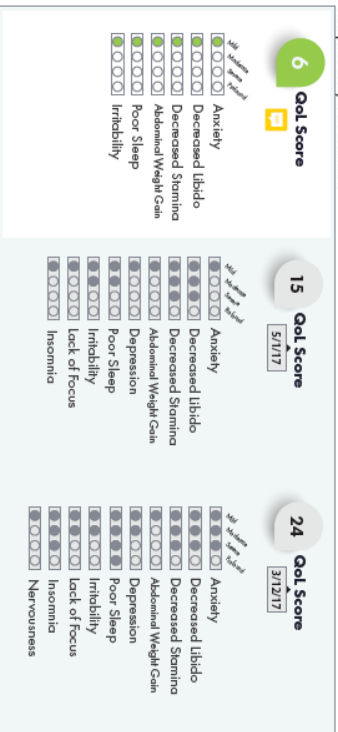
Inhibitory Correlation
Patient indicated symptoms of ANXIETY and IRRITABILITY, which are often the result of decreased inhibitory neurotransmission and/or excess excitatory neurotransmission. As the main inhibitory neurotransmitters, GABA, glycine, and serotonin function to promote calm and prevent over-excitation. GABA is the primary inhibitory neurotransmitter in the CNS and can be thought of as the "great balancer" of the nervous system. Serotonin often functions as a modulator of GABA activity. Either low serotonin or depletion of GABA may cause anxiety.

Unpacking the CARE Package Personalized Correlation Analysis & Education

- Correlates patient complaints listed on their Quality-of-Life Questionnaire with the test results
- Provides in-depth education regarding imbalances and patient symptoms
- Can be shared with patient

Referring Healthcare Provider John Smith, MD 1 Decker Lane San Diego, CA 92160 USA	Date Collected 09/19/2021	Date Reported 09/20/2021	Report Find 09/19/2021	Patient Mary Thompson Report ID: #360785 Gender: F Age: 58
	See Helms Reference Range 09/20/2021			

Self Reported Quality-of-Life Questionnaire



Important Insights

- Since the last half, the patient has seen some concerns diminish completely (excessive appetite, seasonal allergies, night sweats, and nervousness) and a decrease in the severity of other concerns (anxiety, low libido, decreased stamina, abdominal weight gain, depression with nervousness, poor sleep, and irritability). Overall, the patient is showing great improvements.
- Patient has noted they have been diagnosed with one of the AUTISM SPECTRUM DISORDERS. Gender through functional medicine work up to include standard lab testing for autoimmune disease as well as testing for metabolic permeability and comprehensive stool analysis to assess the gut.

Unpacking the CARE Package

Quality-of-Life Score & Insights

- Based on self-reported patient Quality-of-Life Questionnaire
- Shows patient progress based on their own sense of wellness
- Helps to improve compliance
- Shares insights into the patient's quality of life as well as additional impacting factors for your consideration

Referring Healthcare Provider
John Smith, MD
1010 Meridian Ave.
Asheville, NC 28804
USA

Date Collected
09/18/2021
Date Reported
09/20/2021
Set Hormone Reference Range
09/20/2021

Referring
Patient
Mary Thomas
Report ID: #569785
Gender: M
Age: 22

Targeted Nutritional Therapy™ (NTT) Considerations

Proleim™
For insulin support*: S-HF, Sankhomadi, Glycine, Vitamin B6, and Neuro Support Blend®
Targeted Consideration: decrease to x 1 capsule in the PM

Leitra™
For CABA support*: Magnesium, Bioglyceride, Taurine, Sankhomadi, Iodine®, and Neuro Support Blend®
Targeted Consideration: continue with x 1 capsule twice daily

Proctie-DM™
For dopamine support*: Monoamine, N-acetyl-L-tyrosine, D-phenylethylamine, N-Acetyl-L-Cysteine, Quercetin®, Selenium, Vitamin B6, Vitamin B12, Neuro Support Blend®
Targeted Consideration: implement x 1 capsule in the AM

Adaptacin™
For cortisol support*: Borneo natural cortex, Licorice extract, Ashwagandha extract, Rhodiola, Siberian Ginseng Extract, Vitamin C, Panthoic Acid, Magnesium, Zinc, Neuro Support Blend®
Targeted Consideration: decrease to x 1 tablet every other day in the AM

Contegra™
For 5HT function support*: Sankhomadi, N-Acetyl-L-Tyrosine, Siberian Ginseng Extract, Iodine, Betaine, Quercetin®, Vitamin B6, Vitamin B12, Panthoic Acid, Neuro Support Blend®
Targeted Consideration: implement x 1 capsule in the AM

Additional Considerations

Lower insulin dose at onset, consider adjusting eht, and do insulin temp/ incident at home at dose or drop mg/dl.

*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

TARGETED
NUTRITIONAL THERAPY
Sanescor International | 217 West 10th, Asheville, NC 28804 | Phone: 866.637.6295 | support@sanescorhealth.com

Unpacking the CARE Package

Targeted Nutritional Therapy™

- Nutritional formulas recommended based on patient test results and clinical concerns
- Additional nutritional considerations provided

Targeted Nutritional Therapy™

Neuroendocrine Support Formulas*



*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

Quality

Targeted Nutritional Therapy™ (TNT)

- All TNT formulas are manufactured at a cGMP facility
- All TNT formulas are:
 - Free of gluten
 - Non-GMO
 - Free of hydrogenated or partially hydrogenated fats/oils
 - Free of allergens such as:
 - Peanuts, tree nuts, soy, wheat, yeast, shellfish, fish, eggs, artificial preservatives or sugars
- Formulated using high-quality branded ingredients



TARGETED
NUTRITIONAL THERAPY

Quality

NeuroSupport Blend™ (NSB)

- At the base of most TNT™ formulas
- NSB™ - proprietary blend of digestive enzymes, including:
 - Protease
 - Lipase
 - Amylase
- Bioperine® - Enhances the GI uptake of nutrients by:
 - Increasing blood supply to the GI tract*
 - Emulsifying contents of the gut*
 - Actively transporting nutrients across gut wall into bloodstream*



 **BIOPERINE®**

Bioperine® is a registered
trademark of Sabinsa.

Overview

Neurotransmitter Balancing “Filling the Tank”

- Only amino acid precursors replete neurotransmitter reserves
- SSRIs/SNRIs do not “fill the tank” but rather improve neurotransmitter function by slowing neurotransmitter reuptake
- Appropriately balancing hormones will make neurotransmitters work more efficaciously

TNT

Inhibitory Formulas



Prolent™

- Inhibitory formula*
- Support for three inhibitory neurotransmitters (serotonin, GABA, glycine)*
- Vitamins supporting neurotransmitter synthesis*
- NeuroSupport blend



Lentra™

- GABA receptor formula*
- Supports GABA in multiple ways*
- NeuroSupport blend



Tranquilent™

- Chewable inhibitory support*
- Serotonin
- GABA
- Receptor health

TNT

Excitatory Formulas



Contegra™

- HPA-T Balancing Formula*
- Inhibitory/excitatory balance support*
- Thyroid support*
- Adrenal support*
- Methylation support*
- NeuroSupport blend



Procite-D™

- Catecholamine Formula*
 - Catecholamine precursors
 - Vitamins and minerals supporting catecholamine synthesis*
 - Neuroprotectant*
 - NeuroSupport blend

TNT Specialty Formulas



Adaptacin™

- Adrenal support formula*
- Direct cortisol support*
- Adrenal adaptogens*
- Vitamins and minerals support adrenal health*
- NeuroSupport blend



SomniTR™

- Delayed-release sleep formula*
- Direct melatonin support*
- Support for melatonin synthesis*
- GABA support*



MethylMax™

- Comprehensive methylation support formula*
- Key components of the methylation cycle
- Methyl donors*

TNT Tips

Good to Know

- All supplements containing amino acids are best taken on an empty stomach
- "Start low and go slow" philosophy
- Response time varies by patient



Get Started

Implement in Your Practice

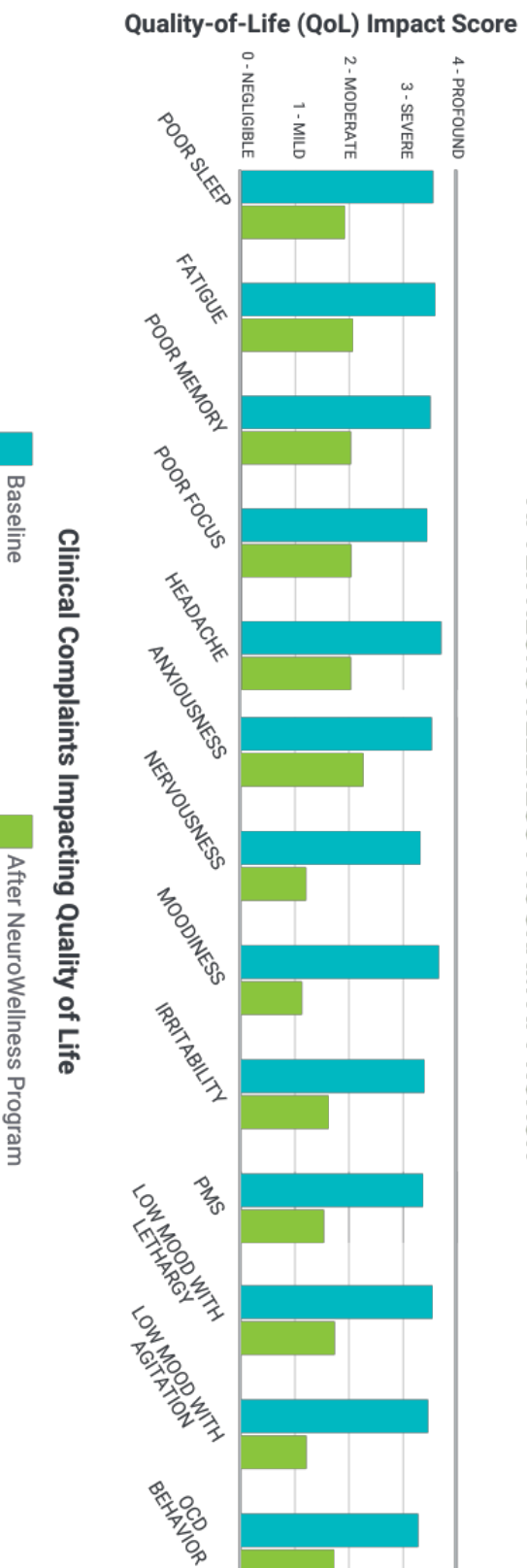
Get Started

Neuroendocrine Balance

- An imbalance in any *one* aspect of neurotransmitter or hormone system leads to a compensatory imbalance of both systems
- **Imbalance perpetuates imbalance**
- Re-establishment of optimal balance **IS possible**
- Assessment is accomplished through serum and saliva hormone levels and urinary levels of Neurotransmitters, along with clinical improvements

Get Started Choose Your Patients

PATIENTS REPORT STATISTICALLY SIGNIFICANT IMPROVEMENTS AFTER NEUROWELLNESS PROGRAM APPROACH



*Self-reported QoL scores on a 4-point Likert Scale, $p < 0.05$

Get Started

Recommended Profiles

HPA-G Complete

7 neurotransmitters

2 adrenal hormones
(4-pt cortisol, 2-pt DHEA-S)

5 sex hormones

Recommended for
individuals >40 years or
experiencing hormone-
related complaints

HPA

7 neurotransmitters

2 adrenal hormones
(4-pt cortisol, 2-pt DHEA-S)

In Summary...

True health is **living well**,
as well as **living longer**.

It is the art of **balance and communication** within the
neuro-endocrine system.

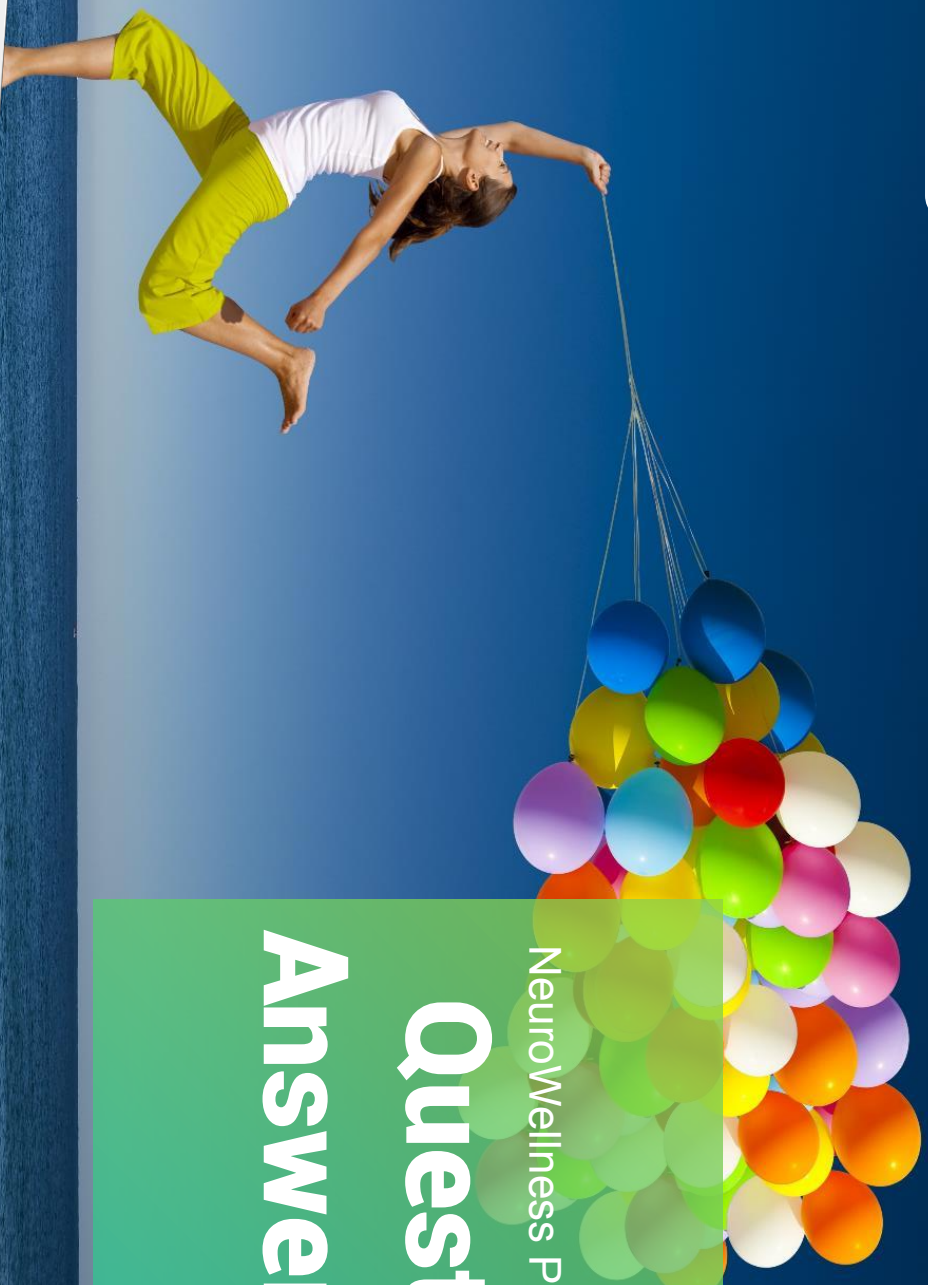


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Thank You So Much!

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May, update image



NeuroWellness Program for Your Practice

Question and Answer Session