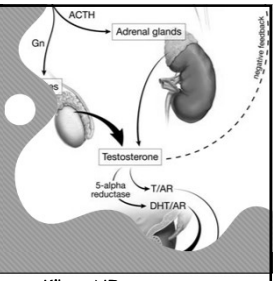
Hormones



Dr Shawna Kiker, ND

The function of hormones on the endocrine system in chronic and neurological disease

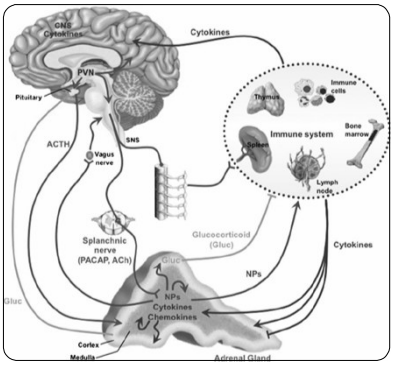
1

It all starts with a healthy…

Hypothalamic-Pituitary-Adrenal Axis

The HPA Axis

- Communication between healthy tissues of the Hypothalamus, Pituitary and the Adrenal glands maintain a healthy Immune System
- This is cytokine mediated and stimulated by adrenal hormones to upregulated the immune response of Macrophages, Neutrophils, Natural Killer (NK) cells and mediates the TH1/TH2 immune response.



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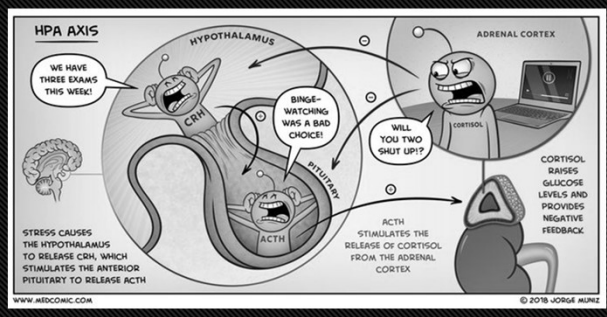

3

It is important to support the HPA axis to maintain a healthy immune response for inflammatory and chronic disease support

The adrenal hormone metabolism in the immune/inflammatory reaction

S R Bornstein [1], H Rutkowski

PMID: **12530688**

Abstract

The interactions between the immune system and HPA axis may be characterized by a circuit which includes; (i) activation of the HPA axis and initiation of the stress response which, in term, has immunomodulating properties; (ii) a feedback mechanism derived from the immune system which regulates the HPA axis. Over the past few years, it has become evident that the adrenal gland, itself, as the main effector organ of the HPA axis, is a major site for both the synthesis and action of numerous cytokines. In addition to the cytokine mediated activation of adrenal regulation there are cytokine independent cell-cell mediated immune-adrenal interactions. The nature of this immune-endocrine crosstalk is implicated in adrenal dysfunction and disease. During inflammatory and autoimmune disorders including sepsis, inflammatory bowel disease and rheumatoid arthritis, the immune-adrenal crosstalk becomes more critical in maintaining an adequate adrenal stress response.

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Stress Depletes Cortisol

Decreased Cortisol decreases Viral Immunity

Chronic Stress depletes Viral Immunity

5

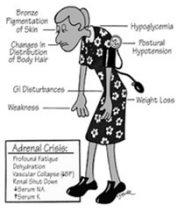
Adrenal Gland Function

Important to the stress response of the body

- If a healthy HPA axis is so critical to a functioning immune system as well as other body systems; we know that a fatigued or dysfunctional HPA axis, such as Adrenal gland dysfunction, leads to a dysfunctional immune response.
- Causes of Adrenal Dysfunction:
  - Prolonged Stress- chemical, mental/emotional, physical
  - Hypoperfusion- Blood Loss
  - Chronic Disease
  - Autoimmune Disorders
  - Long term steroid use or steroid withdrawal
  - Primary Adrenal Insufficiency- Tumor, Addison's Disease
  - Secondary Adrenal Insufficiency- Pituitary Tumor
    - Pituitary Hypoperfusion- Pitocin commonly given post-delivery after blood loss to constrict blood vessels, resulting in temporary to permanent hypoperfusion of the pituitary and dysfunction of many endocrine systems including Adrenal dysfunction.

6

Symptoms and Body Systems Effected by decreased Adrenal hormones



- Thyroid- Graves/Hashimoto's, Temp dysregulation
- Sleep Disturbances- cortisol awakening dysregulation, "wired and tired"
- Brain Fog- Memory Dysfunction
- Adrenaline Dysregulation- adrenaline rushes, fatigue
- Sex Hormone Dysregulation- Endometriosis, PCOS, Uterine Fibroid, Polycystic Breast Dz, decreased libido
- Mitochondrial Dysfunction- fatigue, mineral malabsorption dt hypochlorhydria
- Digestion- Parasites, IBS, allergens and intolerances
- Glucose and Insulin Dysregulation
- Serotonin/Dopamine Production- Anxiety, Depression
- Immune System- Increased risk of cancer, autoimmune and parasitic infections, fibromyalgia
- Neurological abnormalities- Hyper-reflexia, muscle weakness, impaired intelligence and abnormal autonomic function- particularly postural hypotension
- Abdominal Fat, Hair Loss, joint pain, muscle mass loss, dizziness, Electrolyte imbalance, over-exertion with normal exercise and more…

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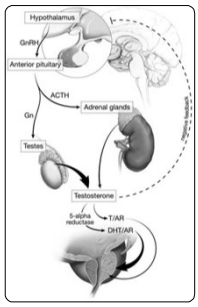
Important to the stress response

Hypothalamic Pituitary Gonadal axis The HPG Axis



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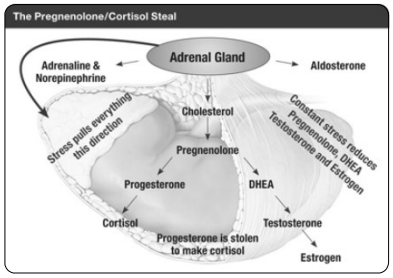

Pregnenolone Steal

Cortisol preservation at Progesterone's Expense

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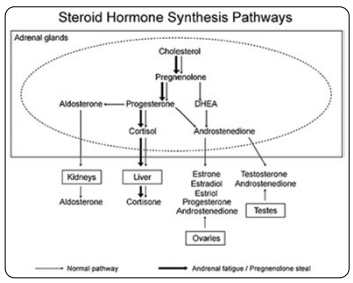
Pregnenolone Dose

- Oral: Empty stomach in the morning
  - Sublingual or Micronized tablet
  - Men: 50-200mg
  - Women: 10-50mg
  - Bipolar Disorders: 500mg/day
- Transdermal Patch:
  - Variants in absorption due to skin hydration
- High dose short term, low dose long term
- Labs: Serum Blood
  - optimal level of serum blood pregnenolone is 180 ng/dL
  - Check before treatment and after 4 weeks of initial treatment

10

Progesterone

- Chronic Stress depletes Progesterone to make up for depleted cortisol levels
- Progesterone modulates GABA receptors in the brain, having a **calming** and **anti-depressant** effect
- Depletion in Progesterone leads to stimulatory effects in the brain and depression.



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Progesterone as NeuroProtective

Progesterone's plausible mechanisms of neuroprotection:

- **Protecting or rebuilding the blood-brain barrier**
- **Decreasing development of cerebral edema**
- **Down-regulating the inflammatory cascade**
- **Limiting cellular necrosis and apoptosis.**

Steroids. 2011 Aug;76(9):845-55
Progesterone inhibition of voltage-gated calcium channels is a potential neuroprotective mechanism against glutamate excitotoxicity.
Neuroscience. 2011 Sep 15;191:101-6
Progesterone in the treatment of acute traumatic brain injury: a clinical perspective and update.
Dialogues Clin Neurosci. 2011;13(3):352-9
Is progesterone a worthy candidate as a novel therapy for traumatic brain injury
1. Ann Emerg Med. 2008 Feb;51(2):164-72
Does progesterone have neuroprotective properties

12

Progesterone and Vitamin D

There are better Neuroprotective effects with Vitamin D than with Progesterone alone!

- Less neuro inflammation
- Less stress on the nervous system
- Better recovery from neurological brain disorders
- Increasing integrity of the blood-brain barrier

Progesterone and Vitamin D

- Neurobiol Aging. 2009 May 29
  Vitamin D deficiency reduces the benefits of progesterone treatment after brain injury in aged rats.
- Mol Med. 2009 Sep-Oct;15(9-10):328-36
  Progesterone with Vitamin D Affords Better Neuroprotection against Excitotoxicity in Cultured Cortical Neurons than Progesterone Alone

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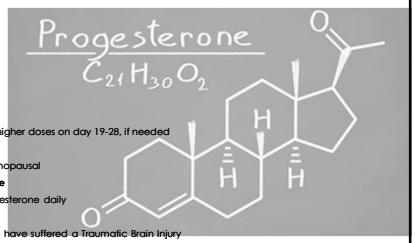
Progesterone Delivery and Dosage

- Oral:
  - Oil suspention drops 4mg/gtt, USP Progesterone
  - SubLingual Troche 50-200 mg
- Pill: 50-200mg, USP Progesterone
- Topical: Cream, Gel, Patch
- Other: IM, IV, pellet



- Cycling Female:
  - Start day 19 to first day of menstruation
  - Can be used all month long, adjusting to higher doses on day 19-28, if needed
- Menopausal Female:
  - Continuous and adjust for cycle if peri-menopausal
- Men: **Use between 10-100mg/day progesterone**
  - Men secrete <3.18 nmol/L (<1 ng/ml) progesterone daily
- Levels over 1200mg/day are given to men who have suffered a Traumatic Brain Injury
- Expect treatment for a minimum of 2-6 months before decreasing or eliminating hormone therapy
- Common Side-Effects patient's notice with too much progesterone- clue to re-do labs!
  - Breast tenderness, Anxiety, Dizziness, wieght gain, water retention

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Progesterone Equivalency

Type	Cyclical Dosage (typical max dose)	Continuous Dosage (typical max dose)
Medroxyprogesterone acetate- oral	5 mg	2.5 mg
Progesterone-Micronized or Sublingual	Up to 200 mg	100 mg
Norethindron acetate-oral	5 mg	2.5 mg
Progesterone- Cream	3% to 20% 3% cream= 30 mg/ml 20% cream= 200mg/ml	1.5% to 10%. 1.5% cream= 15mg/ml 10% cream= 100mg/ml (or gram)
Norethindrone- oral	.7 mg	.35 mg
Progesterone gel 4%	Continuous Dosing Every other day for 12 days (delivers 45 mg of progesterone per application) 2 times weekly	

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Progesterone Labs

Check	Before treatment
	4 weeks after initial treatment or changes in hormone treatment
	Every 3-6 months after that for duration of treatment

Progesterone	Serum Blood		Saliva (10-12x more sensitive)	
Women	ng/ml	nmol/L	pg/ml	pmol/L
Follicular	<1	<3.18	12-100	38 - 318
Luteal	5 – 20	15.9 - 63.6	75 - 270	238.5 – 858.5
Postmenopausal	< 1	<3.18	12-100	38 - 318
Men	< 1 ng/ml	<3.18 nmol/L	15-100	47.7 – 318

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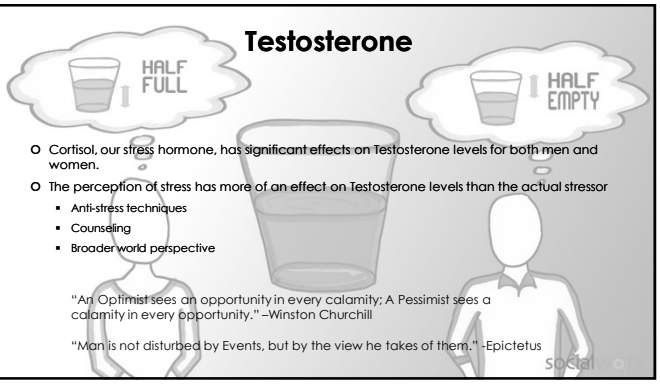
Testosterone



- Cortisol, our stress hormone, has significant effects on Testosterone levels for both men and women.
- The perception of stress has more of an effect on Testosterone levels than the actual stressor
  - Anti-stress techniques
  - Counseling
  - Broader world perspective

"An Optimist sees an opportunity in every calamity; A Pessimist sees a calamity in every opportunity." –Winston Churchill

"Man is not disturbed by Events, but by the view he takes of them." -Epictetus

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Testosterone Deficiency

Men	Women
Low libido	**Low libido**
Low Energy	**Low Energy**
Eight gain – loss of muscle mass	**Weight gain - loss of muscle mass**
Hypogonadism	**Loss of bone density**
Erectile Dysfunction	**Depression**
Low sense of well being	**Low sense of well-being**
Low Sperm count	**Stress incontinence**
Decrease in bone density	**Decreased motivation for change**
Mood Changes	**Estrogen Dominance SX**
Memory loss	**Memory Loss**
Hair Loss	**Hair Loss**
Elevated Cholesterol- Hypercholesterolemia	
Anemia	

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Testosterone Delivery and Dosage

Refer to labs and patient symptoms for dosage and frequency

Women

- SubQ: 5-10mg every 7-10days, Dermal or SubQ injection
- IM: Cypionate 10-25mg every 7-10 days, deep muscle
  - Testosterone levels peak after day 2-3 of the injection and then slowly fall back down over the next 4-5 days
- 1% Cream: 5mg-10mg, daily topical
  - May require higher doses and changes in dosing over time
  - Absorption varies between individuals and skin hydration

Side Effects and Symptoms of too much Testosterone

- Hypertension
- Irritability
- Mentrual Irregularities
- Absent Period
- Hirsutism
- Enlarged Clitoris
- Balding- Hairline
- Increase Muscle Mass
- Decreased Breast Size
- Change in Body Shape
- Oily Skin
- Deeper Voice
- Excess Body Hair

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Testosterone in Women

- Harvard Health Publishing, Women's Health
- **Study identifies effective testosterone dose for women**
- October 16, 2014
- Testosterone applied to the skin has been demonstrated to improve sex drive in women. However, there has been uncertainty about the optimal dose—one that works well without unacceptable side effects.
- A study in the journal *Menopause*, published online in August, may fill that void. Researchers in Australia tested **both 5-mg and 10-mg doses of a standardized 1% testosterone cream** in seven healthy postmenopausal women with imperceptible blood levels of testosterone. They found that applying the 5-mg dose to the upper arm daily for six weeks brought testosterone levels back into the normal premenopausal range, while using the 10-mg dose elevated levels above the premenopausal range. Neither dose was associated with masculinizing side effects.

As a general rule, if you have a woman who is symptomatic with testosterone levels in the bottom 50% of the reference range then you should consider testosterone replacement therapy

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Testosterone Delivery and Dosage

Refer to labs and patient symptoms for dosage and frequency

Men

- IM: Cypionate 100-200mg every 7-10 days, deep muscle
  - Testosterone levels peak after day 2-3 of the injection and then slowly fall back down over the next 4-5 days
- 5-20% Cream/Gel: 5mg-10mg/ml, daily topical
  - May require higher doses and changes in dosing over time
  - Absorption varies between individuals and skin hydration
- Oral: Not an option due to liver toxic effects of 1st pass metabolism

Side Effects and Symptoms of too much Testosterone

- Hypertension
- Irritable and Emotional
- Decreased Sperm Count
- Balding
- Increase Muscle Mass
- Oily Skin
- Deeper Voice
- Excess Body Hair
- Increased Sex Drive
- Sleep Apnea
- Breast Enlargement
- Liver disease
- Depression
- Headaches

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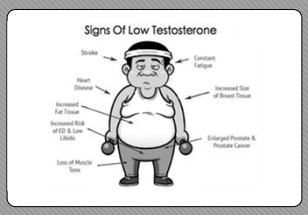

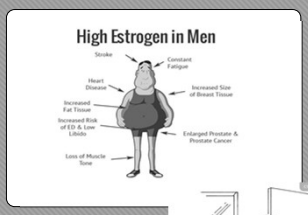

Estrogen

The Goldilocks Hormone-
Not to high, not too low, but just right!

"I'm sure menopause is no fun, but look on the bright side...beards are in fashion right now."

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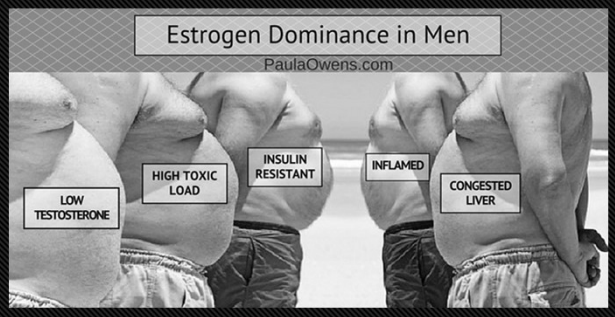

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Estrogen Dominance

Men	Women
Heart Disease	Thyroid Disease
Stroke	Stroke
Erectile Dysfunction	Auto-Immune Disease
Low libido	Low Libido
Weight gain, low muscle mass	Weight gain
Prostate Dysfunction and Cancer	Breast, Uterine Cancer
Fatigue	Fatigue
Gynecomastia	Fibroids, Endometriosis, PMS, PCOS
Mood Swings	Mood Swings
	Hair Loss
	Migraines/Headaches

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Estrogen Dominance and Neurological Disorders

- COMT gene mutations can also cause high or low dopamine levels
  - High:
    - Amine containing foods with tryptophan, tyrosine, phenylalanine- turkey, cheese
    - Smoking, Alcohol, Caffeine

High Dopamine	Low Dopamine
Aggressive tendencies	Addiction
Violent Behavior	Low Libido
Impulsivity	Depression
Schizophrenia	Tremors
	Mental and Physical Fatigue

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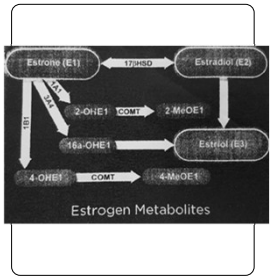
Metabolism of Estrogen- The Goldilocks Hormone

- COMT SNPs-

  Help understand how much support the Estrogen pathways may need and why Estrogen metabolism favors inflammatory estrogen metabolism.
- Low levels of E1 converting to 2-OHE1 and 4–OHE1 compared to 16-OHE1= Low Methylation
- 2-Hydroxyestrone (2-OHE1) / 2-Methoxyestrone (2-OMeE1), High ratio= Low Methylation
- 2/16 Hydroxyestrogen Ratio- High 16-a-OHE1 with low 2–OHE1, driving ratio to be low= Low Methylation
- Indole-3-Carbonol- Has been shown to reduce 16a-OHE1 and increasing 2–OHE1
- Methylators- Folate and B12, SAMe, Betaine & Glycine, B6 and Mg are also helpful!



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Estrogen Dominance Treatment Options

- **Methylators- Folate and B12, SAMe, Betaine & Glycine, B6 and Mg are also helpful!**

WARNING!

COMT mutations

The problem is not the lack of precursors! It is a genetically predisposed slow producing enzyme. This group of patients still NEED methylation support but at low frequent dosing as to not overwhelm the COMT enzyme

- **Low dose SAMe, Mg and B12 in frequent dosing** works great!
- **Aromatase Inhibitors**
- **Indole-3-Carbonol 400-800mg/day**
  - Has been shown to reduce 16a-OHE1 and increasing 2–OHE1
  - Important to include methylation support if COMT SNP mutations exist
  - Needs Normal stomach pH to convert to active DIM
  - Can increase Testosterone
- **DIM- safe in doses up to 600mg/day**
  - Safer, more stable and more research with DIM
  - Can increase Testosterone
- **Fiber**
  - Decreases the available Estrogen for reabsorption from the gut back to the liver.
  - Provides Pre-biotics for healthy gut bacteria

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Estrogen- The Goldilocks Hormone

Too Much you get cancer; Not enough you get cardiovascular disease

The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy

- There are controversies surrounding the clinical use of exogenous Estradiol as a therapeutic agent for cardiovascular disease in women due to the possible risks of thrombotic events, cancers, and arrhythmia
- **It has also been shown to significantly reduce cardiovascular events and is a non-invasive and non-expensive treatment option**

Studies in 2017, suggested that Estradiol started in the perimenopausal or early postmenopausal period is cardioprotective, whereas Estradiol begun late after menopause increases the risk of CVD

29

Estrogen Use in Neurological Disorders

- Estrogens prevent and controls the inflammatory response in the manifestation and progression of pathologies, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease

Endocr Rev. 2016 Aug; 37(4): 372–402. Published online 2016 May 19. PMID: 27196727
Estrogens, Neuroinflammation, and Neurodegeneration, Alessandro Villa, Elisabetta Vegeto, Angelo Poletti, and Adriana Maggi

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Estrogen Deficiency- Women

Women	
Vaginal Dryness	
PMS	Depression dt decrease of Serotonin
Hot Flashes	Parkinson's and Alzheimer's Dz
Urinary Incontinence, UTI's	Decreased HDL Cholesterol
Heart Palpitations, Heart Disease	Decreased Bone Density
Memory Loss	Decrease in Cognitive Function
Joint Pain- mimicking Arthritis	
Tinnitus	Estrogen is neuroprotective from Epilepsy
Burning Tongue	Estrogen is neuroprotective in Brain Injury
Brittle Nails	Estrogen is neuroprotective in degenerative brain disorders

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Neuroprotective Effects of Estrogen

Neural Regen Res. 2017 Nov; 12(11): 1799–1800.

doi: 10.4103/1673-5374.219036

PMCID: PMC5745828

PMID: 29239320

Outlook on the neuroprotective effect of estrogen

Xavier d'Anglemont de Tassigny*

Author information Article notes Copyright and License information Disclaimer

This short review will summarize the current knowledge in estrogen therapy with particular focus on some of the recent work that might lead to new neuroprotective treatments.

Neuroprotective properties of estrogen in brain injury and neurodegenerative diseases: …estrogen has positive impact on general cognitive function, and the experimental and clinical cases that link estrogen concentration to brain protection are plentiful.

Conclusion: The neuroprotective effect of estrogen is as tangible as it is naïve. On one hand, converging evidence from clinical observations and experimental studies support the use of estrogenic compounds to prevent or moderate the brain tissue damage. On the other hand, the complexity of estrogenic actions throughout the body makes estrogen therapy a rather unspecific and challenging treatment for the injured brain. Consequently, finding the specific intracellular mechanisms promoted by estrogen stimulation may help to optimally tune the cell homeostasis and raise protective shields to prevent the CNS and PNS damage occurring after nerve injury, or in a disease. Thus, a neuroprotective strategy based on estrogen treatment is conceivable, although much effort has to be made before this can be achieved.

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Neuroprotective Implications of Estrogen

Alzheimer's Dz

- Estrogen for Alzheimer's disease in womenRandomized, double-blind, placebo-controlled trial V.W. Henderson, A. Paganini-Hill, B.L. Miller, et al., January 25, 2000
- The role of estrogen in the treatment of Alzheimer's disease Stanley J. Birge, May 01, 1997
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- Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease Lon S. Schneider, Martin R. Farlow, Victor W. Henderson, et al., June 01, 1996

Migraines

- Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen E. A. MacGregor, A. Frith, J. Ellis, et al., September 13, 2006

Alzheimer's Dz- decreased incidence of Dementia

- Postmenopausal estrogen use and Parkinson's disease with and without dementia K. Marder, M.-X. Tang, B. Alfaro, et al., Neurology April 01, 1998

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Estrogen Delivery and Dosage

Refer to labs and patient symptoms for dosage and frequency

Compound	Type of Estrogen	Typical Dose	Comments
Conjugated Estrogens	Oral	0.625 mg, daily	Pregnant mare urine, converted to Estrone
Ethinyl Estradiol	Oral Estradiol	0.02-0.05 mg daily	
Micronized Estradiol	Oral Estradiol	0.5-2.0 mg	
Estrones	Oral Estrone	0.625-2.5 mg	
Compounded Estrogens	Tri-Estrogen	10% E1 10% E2 80% E3	Compounding Pharmacy
Estrogen Patch	Once per week Estradiol	0.05mg/week	Systemic, even level of Estradiol
	Twice per week	0.05mg twice/week	Systemic, even level of Estradiol
Vaginal Cream	Estradiol	0.01% Vaginal Cream 1-4g/day	Treats vaginal dryness
Pellets	Estradiol/Estriol	12.5mg every 4 months	Risk of infection at insertion site 4 month commitment to dose
Oral Contraceptives	Varies Estrogen/Progesterone		Not for HRT due to the high progesterone levels
Soy Products	Phytoestrogens		Alternative to drugs, high in calories

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