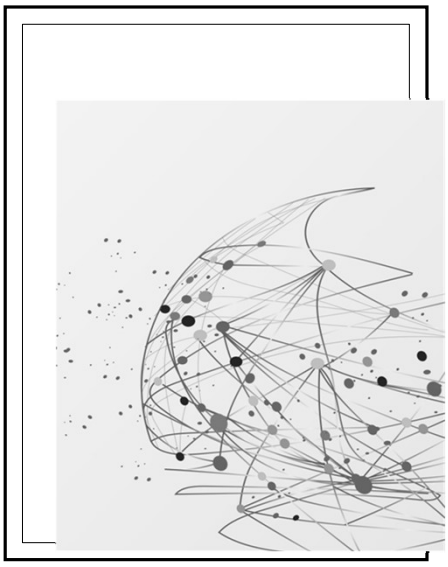

EVERYTHING HORMONES

CHICAGO 2023

Dr. Devaki Lindsey Berkson &
Metabolic Maintenance

2023

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EVERYTHING HORMONES

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AMERICAN COLLEGE OF OBSTETRICS & GYNECOLOGY POSITION STATEMENT ON BIOIDENTICAL HORMONES

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 532 • August 2012 *(Replaces No. 387, November 2007 and No. 322, November 2005)*
Reaffirmed 2020

Committee on Gynecologic Practice and the American Society for Reproductive Medicine Practice Committee

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Compounded Bioidentical Menopausal Hormone Therapy

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ACOG

Compounded Bioidentical Menopausal Hormone Therapy

ABSTRACT: Although improvement in long-term health is no longer an indication for menopausal hormone therapy, evidence supporting fewer adverse events in younger women, combined with its high overall effectiveness, has reinforced its usefulness for short-term treatment of menopausal symptoms. Menopausal therapy has been provided not only by commercially available products but also by compounding, or creation of an individualized preparation in response to a health care provider's prescription to create a medication tailored to the specialized needs of an individual patient. The Women's Health Initiative findings, coupled with an increase in the direct-to-consumer marketing and media promotion of compounded bioidentical hormonal preparations as safe and effective alternatives to conventional menopausal hormone therapy, have led to a recent increase in the popularity of compounded bioidentical hormones as well as an increase in questions about the use of these preparations. Not only is evidence lacking to support superiority claims of compounded bioidentical hormones over conventional menopausal hormone therapy, but these claims also pose the additional risks of variable purity and potency and lack efficacy and safety data. The Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists and the Practice Committee of the American Society for Reproductive Medicine provide an overview of the major issues of concern surrounding compounded bioidentical menopausal hormone therapy and provide recommendations for patient counseling.

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Background

Before the publication of the Women's Health Initiative (WHI) findings, it was believed that "replacing" lost ovarian hormones would not only relieve menopausal symptoms but also improve overall health. This belief was dispelled after the WHI reported a lack of cardioprotection and an increased risk of incident breast cancer (1), venous thromboembolism (1), and stroke (2) associated with the use of combined hormone therapy. These findings dramatically changed the indications for menopausal hormone therapy, and secondary analysis of WHI results continues. Although improvement in long-term health is no longer an indication for menopausal hormone therapy,

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Compounded Bioidentical Hormones

Bioidentical hormones are plant-derived hormones that are chemically similar or structurally identical to those produced by the body. Bioidentical hormones include commercially available products approved by the U.S. Food and Drug Administration (FDA), such as micronized progesterone and estradiol, as well as compounded preparations that are not regulated by the FDA. Many compounding pharmacies use the term bioidentical hormone to imply that these preparations are natural or the same as endogenous substances and, thus, are safe. The phrase bioidentical hormone therapy has been recognized by the FDA and the Endocrine Society as a marketing term and not one based on scientific evidence (4).

Examples of compounded hormones include Biest (biestrogen) and Triest (triestrogen) preparations. The name Biest commonly refers to an estrogen preparation based on a ratio of 20% estradiol and 80% estriol on a milligram-per-milligram basis. A similar preparation, Triest, usually contains a ratio of 10% estradiol, 10% estrone, and 80% estriol. These ratios are not based on each agent's estrogenic potency but on the milligram quantity of the different agents added together (5). Other commonly compounded hormones include dehydro-

The practice of custom blending commercially available drug products may lack both a strong biological rationale and medical evidence for effectiveness. Moreover, it introduces the possibility of multiple sources for drug effects and adverse effects, making it difficult to identify the active agent responsible. For these reasons, compounded preparations generally are considered inferior to FDA-approved agents, which have much better characterized pharmacokinetic properties.

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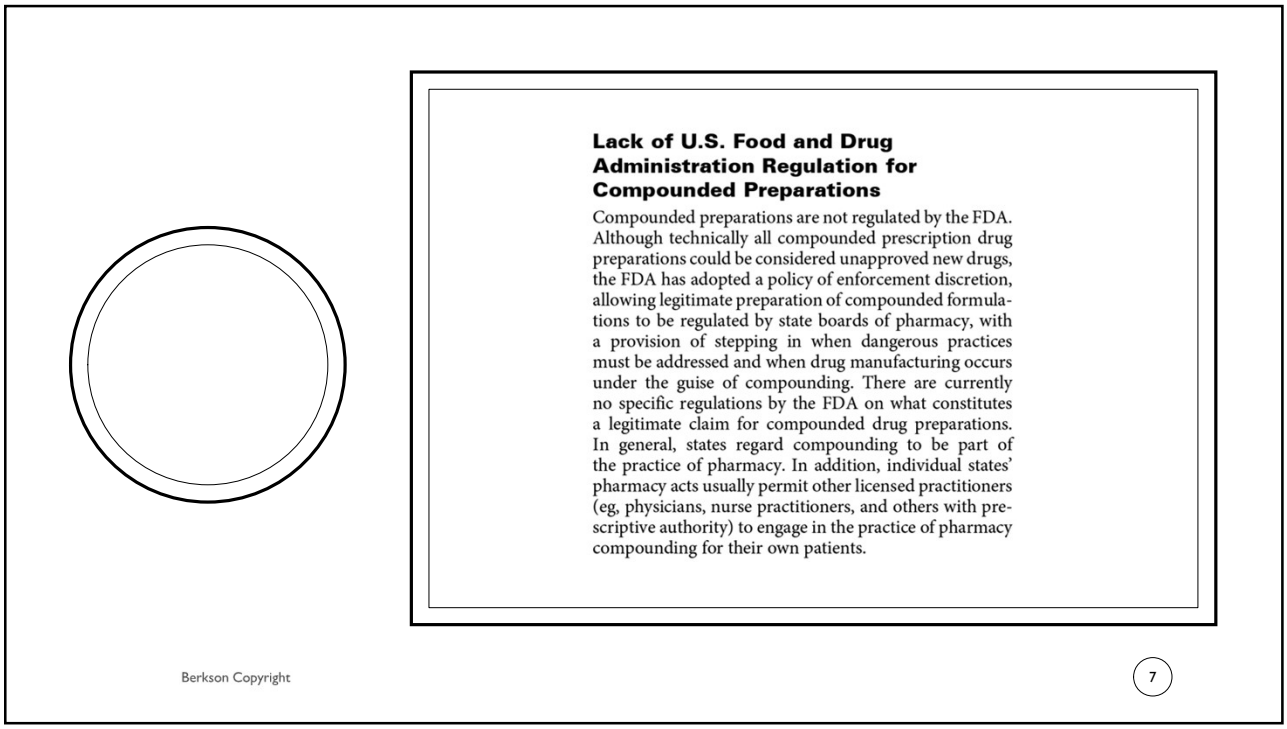
Lack of U.S. Food and Drug Administration Regulation for Compounded Preparations
Compounded preparations are not regulated by the FDA. Although technically all compounded prescription drug preparations could be considered unapproved new drugs, the FDA has adopted a policy of enforcement discretion, allowing legitimate preparation of compounded formulations to be regulated by state boards of pharmacy, with a provision of stepping in when dangerous practices must be addressed and when drug manufacturing occurs under the guise of compounding. There are currently no specific regulations by the FDA on what constitutes a legitimate claim for compounded drug preparations. In general, states regard compounding to be part of the practice of pharmacy. In addition, individual states' pharmacy acts usually permit other licensed practitioners (eg, physicians, nurse practitioners, and others with prescriptive authority) to engage in the practice of pharmacy compounding for their own patients.
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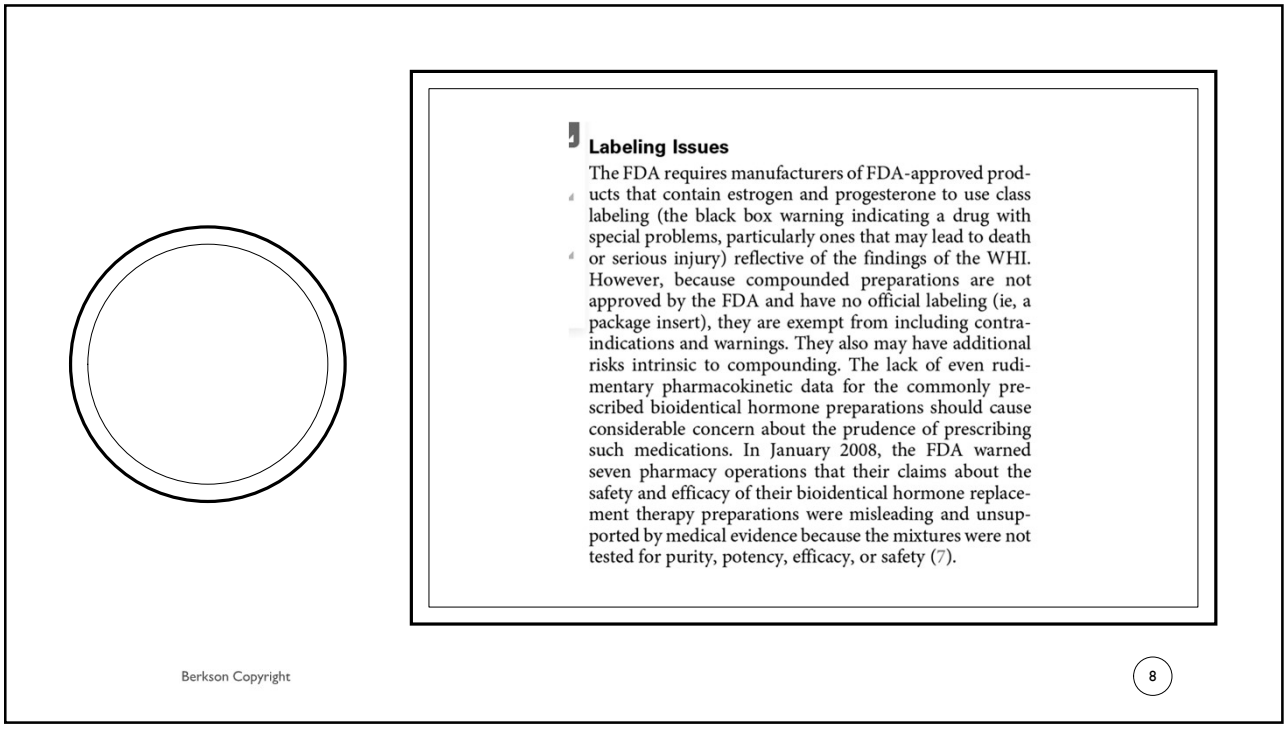
Labeling Issues
The FDA requires manufacturers of FDA-approved products that contain estrogen and progesterone to use class labeling (the black box warning indicating a drug with special problems, particularly ones that may lead to death or serious injury) reflective of the findings of the WHI. However, because compounded preparations are not approved by the FDA and have no official labeling (ie, a package insert), they are exempt from including contraindications and warnings. They also may have additional risks intrinsic to compounding. The lack of even rudimentary pharmacokinetic data for the commonly prescribed bioidentical hormone preparations should cause considerable concern about the prudence of prescribing such medications. In January 2008, the FDA warned seven pharmacy operations that their claims about the safety and efficacy of their bioidentical hormone replacement therapy preparations were misleading and unsupported by medical evidence because the mixtures were not tested for purity, potency, efficacy, or safety (7).
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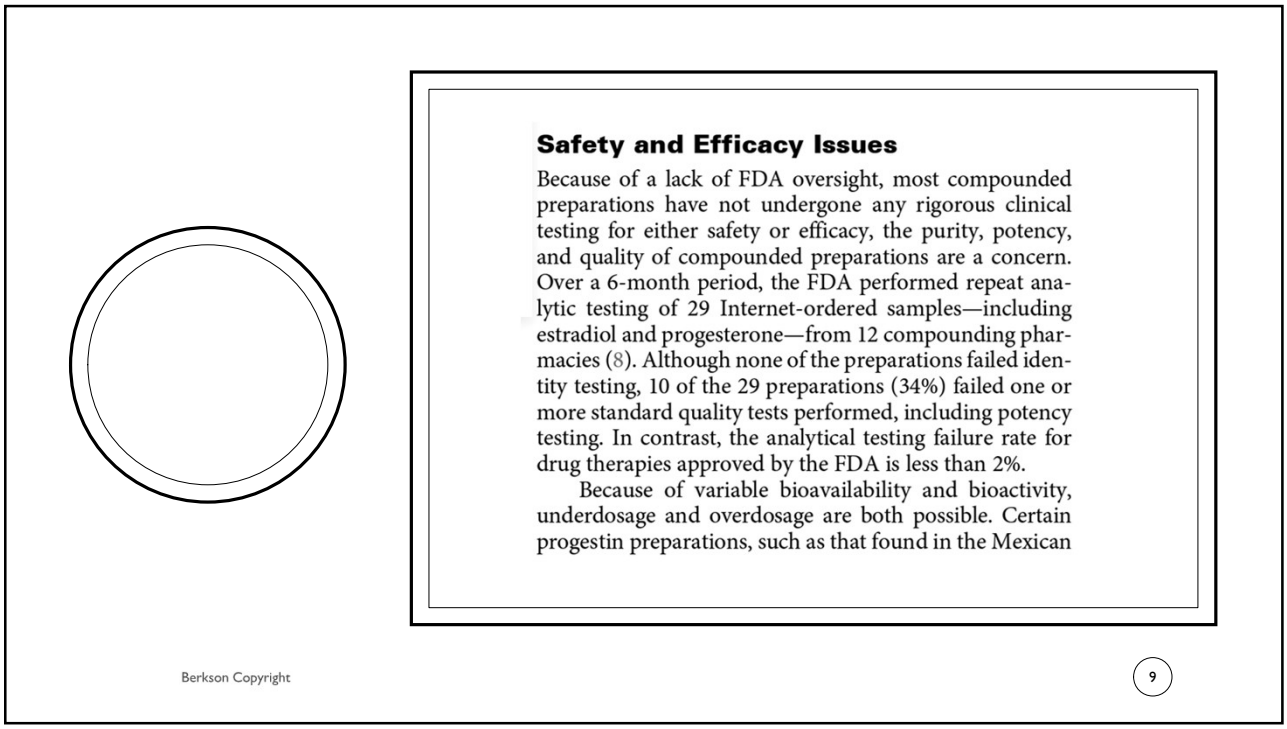
Safety and Efficacy Issues
Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, the purity, potency, and quality of compounded preparations are a concern. Over a 6-month period, the FDA performed repeat analytic testing of 29 Internet-ordered samples—including estradiol and progesterone—from 12 compounding pharmacies (8). Although none of the preparations failed identity testing, 10 of the 29 preparations (34%) failed one or more standard quality tests performed, including potency testing. In contrast, the analytical testing failure rate for drug therapies approved by the FDA is less than 2%.
Because of variable bioavailability and bioactivity, underdosage and overdosage are both possible. Certain progestin preparations, such as that found in the Mexican
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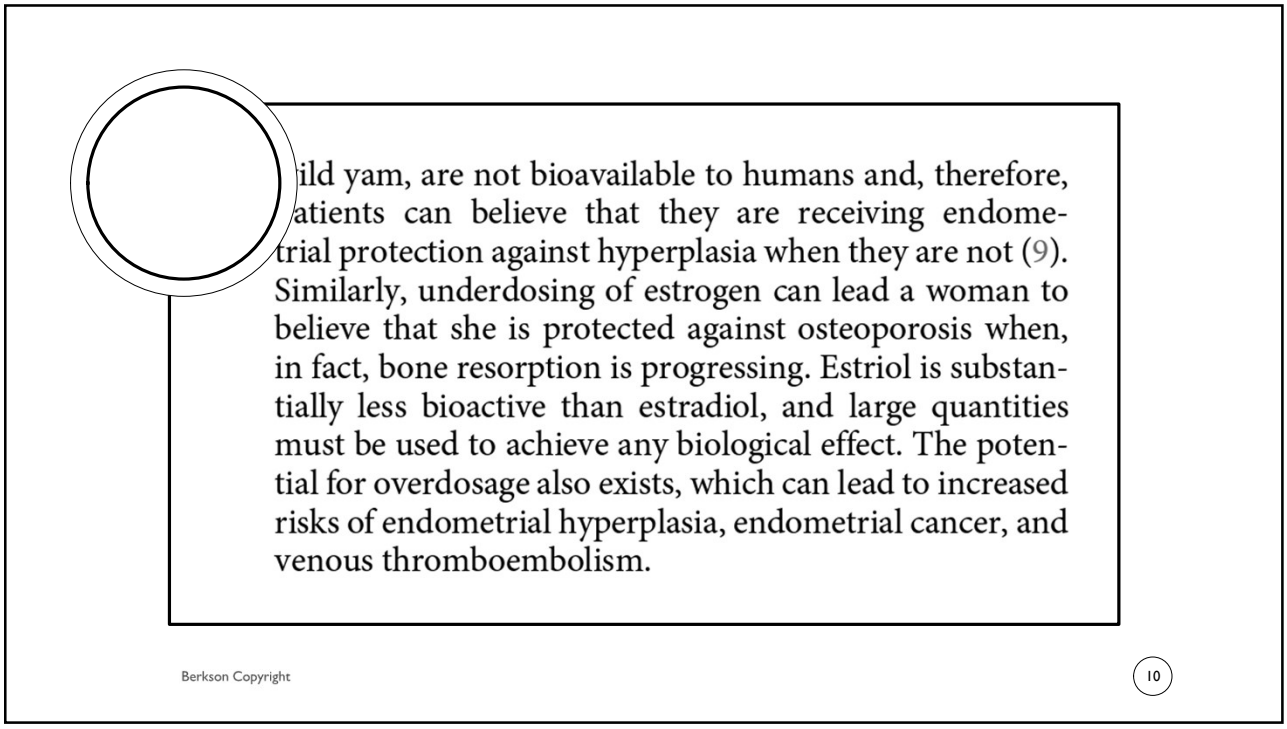
ild yam, are not bioavailable to humans and, therefore, atients can believe that they are receiving endometrial protection against hyperplasia when they are not (9). Similarly, underdosing of estrogen can lead a woman to believe that she is protected against osteoporosis when, in fact, bone resorption is progressing. Estriol is substantially less bioactive than estradiol, and large quantities must be used to achieve any biological effect. The potential for overdosage also exists, which can lead to increased risks of endometrial hyperplasia, endometrial cancer, and venous thromboembolism.
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WHY WOULD MOTHER NATURE

- Make the very molecules that "drive" humanity
- Hormones
- Be pro-carcinogenic?

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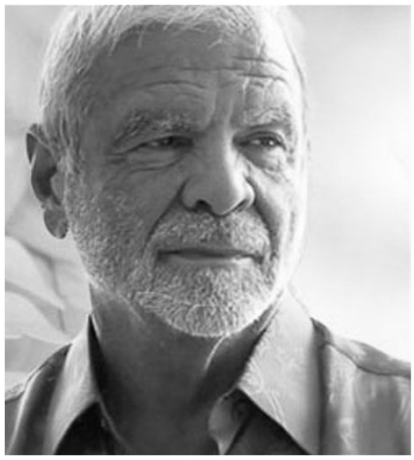
All our careers have their own "Fickle fingers of fate".

- **Jonathan V. Wright MD**
- **"Father of Bioidentical**
- **Hormones"**



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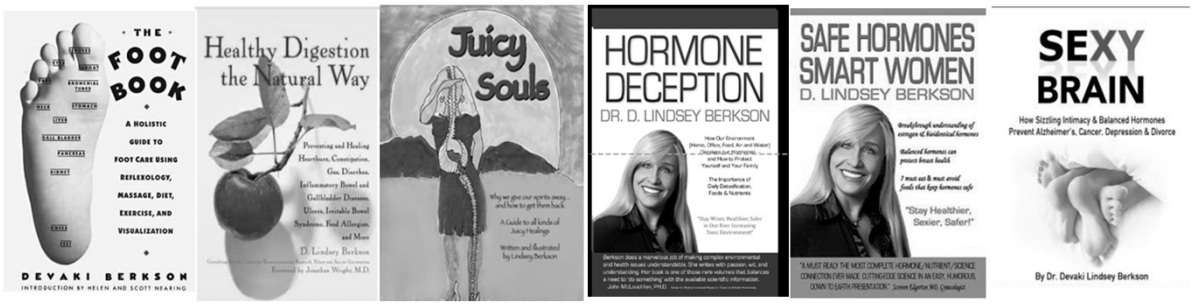

MEET THE FAMILY

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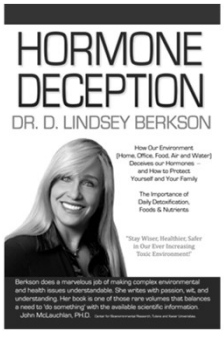
WHY AM I GIVING THIS TALK?

BASED ON THIS BOOK INVITED TO BE A HORMONE SCHOLAR AT TULANE:

CENTER FOR BIOENVIRONMENTAL RESEARCH



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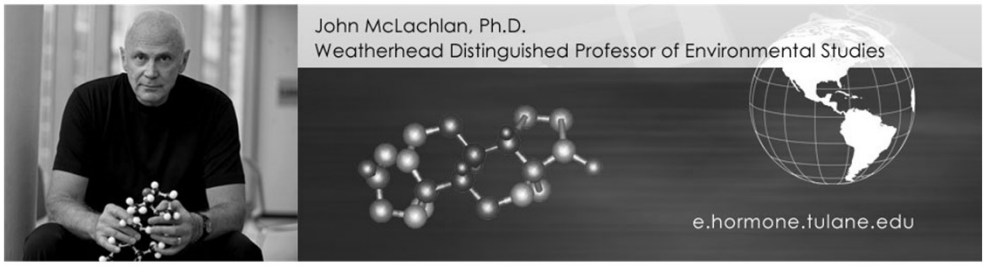
HORMONE SCHOLAR
AT CENTER FOR BIOENVIRONMENTAL RESEARCH - ENVIRONMENTAL ESTROGEN THINK TANK.



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MENTOR/MENTEE

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GOT TO HANG WITH RECEPTOR SCIENTISTS

Elwood Jensen ER alpha

Dr. Jan-ake Gustafson –ER beta

17

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Receptors = malleable as built to "receive"

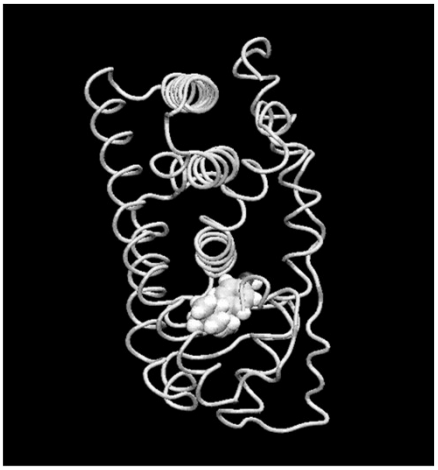

Image courtesy of T. Bishop, CBR

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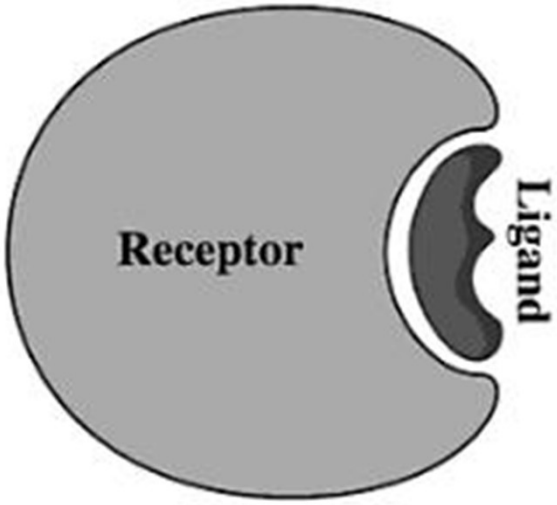

TARGET TISSUES HAVE RECEPTORS

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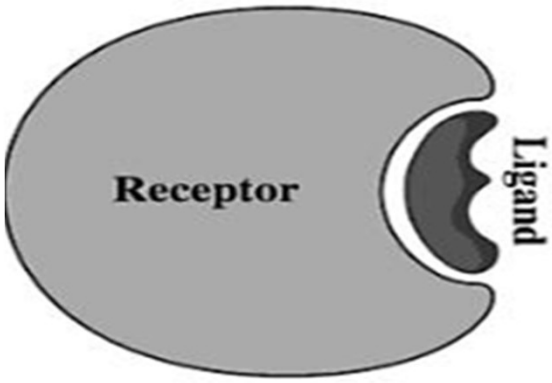
RECEPTOR FUNCTIONALITY DEPENDS ON NUTRIENTS



Nutrient Bowl

- Zinc (fingers)
- Vitamin B6
- Magnesium
- Iodine
- Vitamin A
- Boron

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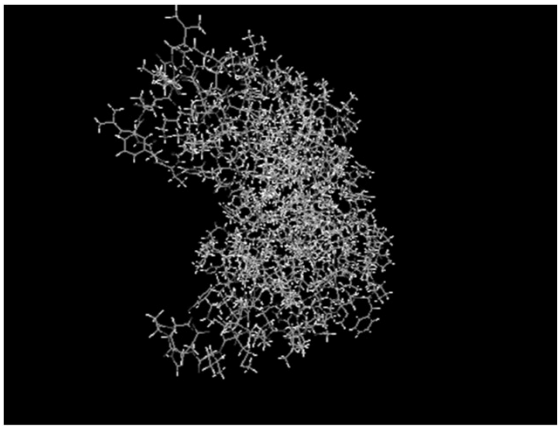
TARGET TISSUE
MOVIES: HORMONES DOCKING



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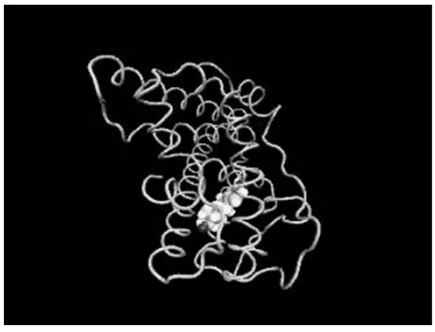
B_6 – TIMING IS EVERYTHING –
DIFFERENCE BETWEEN ESTROGEN DOMINANCE & BALANCE



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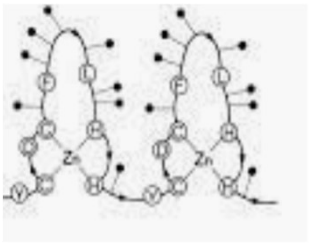
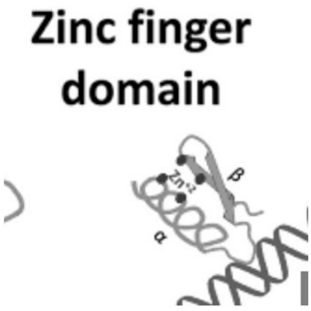
ZINC GIVES SHAPE SO LIGANDS (HORMONES) CAN DOCK SO PERFECT ASSAYS OF HORMONES BY ANY TESTING MEAN LITTLE WITH LOW RBC ZINC





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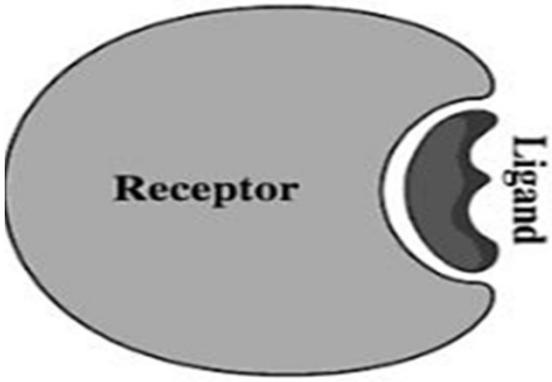
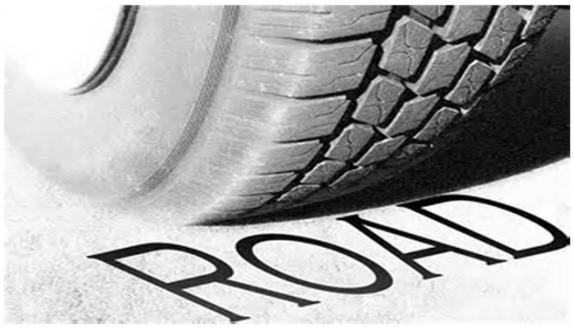
RECEPTOR FUNCTIONALITY

POOR DIET >>> POOR RECEPTOR FUNCTIONALITY

Receptor Functionality



Is where the hormone rubber meets the hormone road.



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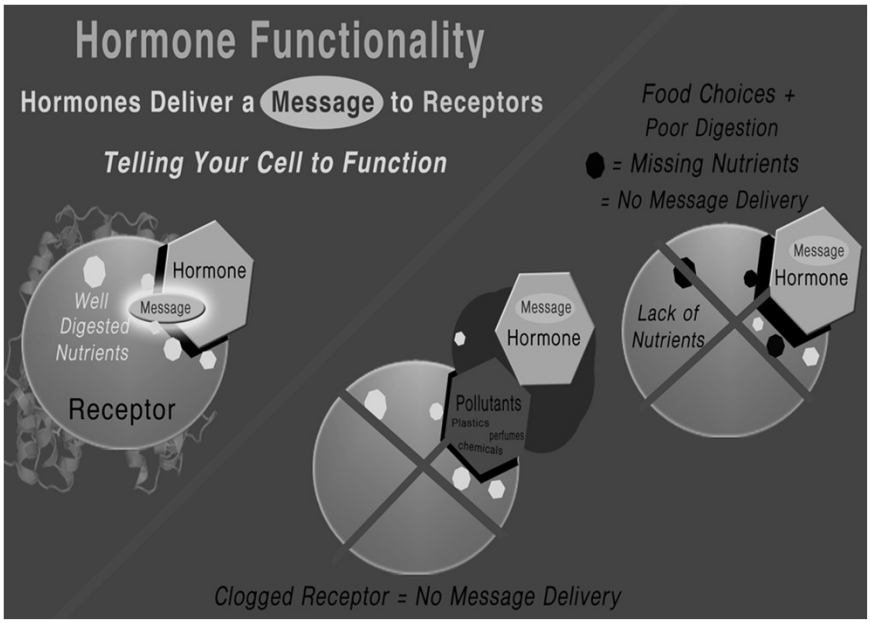

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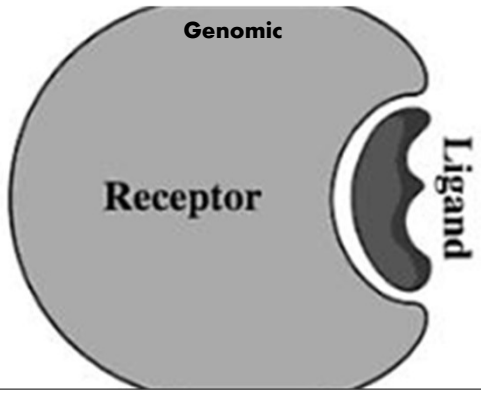
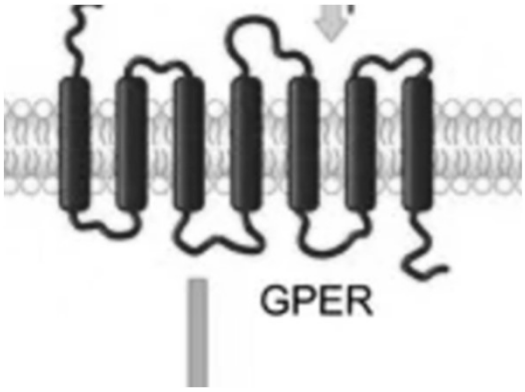
HORMONE SIGNALING



Hormone binds to cytoplasmic receptor – genomic ER alpha ER beta receptors Estrogen signaling multiple pathways to impact gene transcription. Curr Genomics. 2006;7(8):497-508.



Hormone binds to membrane – non-genomic G-Protein Coupled Estrogen Receptor

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NUTRITION EFFECTS BOTH FORMS OF SIGNALING THOUGH NOT APPRECIATED

- **Genomic Signaling**
- **Needs receptor to be "available"**
- **No endocrine disruptors**
- **No excess cortisol**
- **No excess chemicals**
- **Zinc fingers allow ligand to dock**
- **B_6 controls duration of signal**
- **Transcriptional co-factors (iodine, retinoic acid, magnesium, Vit C)**

- **Non-genomic Signaling**
- **Needs fluid membranes**
- **EFA balance of 3:6**
- **No hardening of fats**
- **No trans-fatty acids**

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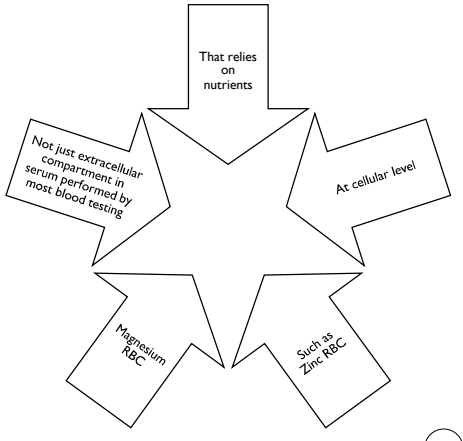
HORMONE BIGGER PICTURE FEW DOCS TAKE INTO ACCOUNT

- Not just about levels
- Tested and debated in blood, saliva, urine, etc.
- There is a bigger picture



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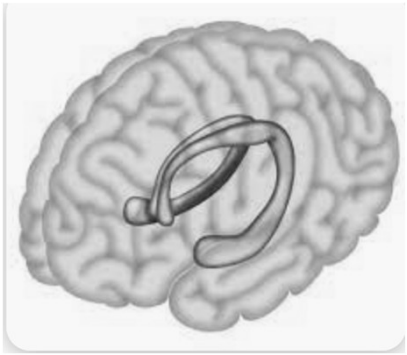
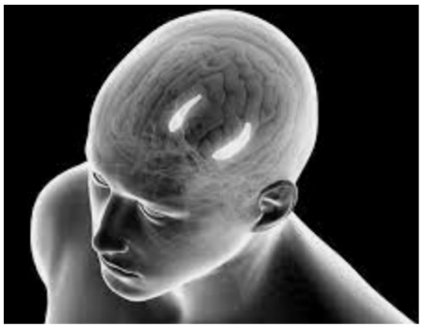
KEEPING YOUR WITS ABOUT YOU IS KEEPING YOUR HIPPOCAMPUS VOLUME





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EXERCISE, MEDITATION VS. HORMONES?

- **Yales' MEDEX study**
- **Yale School of Medicine took this challenge on, using intense mindfulness versus physical exercise, to see if either could reboot the hippocampus. And thus protect memories and slow down the aging of the brain.**
- **The interventions were intense.**
- **The exercise group did a total of 300 minutes of weekly exercise.**
- **The mindfulness program was characterized by 8 weekly classes of 2.5 hours each as well as a half-day retreat and 60 additional minutes daily, to teach mindfulness and meditation**
- **What happened to the hippocampus?**
- **Did exercise or mindfulness boost its volume and protect cognition?**
- **NO!**
- **How did they figure this out? Researchers used MRIs to measure the hippocampal volume.**
- **In both groups. Hippocampal volume went down.**

- Mindfulness, Exercise Strike Out in Memory Trial - *Medscape* - Dec 13, 2022.

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HRT AND HIPPOCAMPAL VOLUME MCGILL UNIVERSITY

- **Catherine Lord Ph.D. from the Department of Neuroscience at McGill University wrote in 2007, in Chapter 3 of her thesis for her Ph.D.:**
- **"HIPPOCAMPAL VOLUMES ARE LARGER IN POSTMENOPAUSAL WOMEN USING ESTROGEN THERAPY COMPARED TO PAST USERS, NEVER USERS AND MEN: A POSSIBLE WINDOW OF OPPORTUNITY EFFECT!"**
- **Two U.S. departments of neuroscience and cognitive medicine wrote that estrogen administration following menopause has been shown to support hippocampally mediated cognitive processes.**
- **1.5 mg of E_2/d is the dose while 1 mg did not in all.**
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.

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CACHE COUNTY STUDY

- Prospective study of incident dementia among 1357 men (mean age, 73.2 years) and 1889 women (mean age, 74.5 years) residing in a single county in Utah. Participants were first assessed in 1995-1997, with follow-up conducted in 1998-2000. History of women's current and former use of HRT, as well as of calcium and multivitamin supplements, was ascertained at the initial contact.
- Women on 10 years of ER had 30 to 50% decreased incidence of Alzheimer's Dx.
- **Results:** Women who used any type of HT within 5 years of menopause had 30% less risk of AD (95% confidence interval 0.49-0.99), especially if use was for 10 or more years.
- Use in later life, especially if oral or progestin, linked to increased risk.
- **Conclusions:** Our results suggest that longer EEE and HT use, especially in older women, are associated with higher cognitive status in late life
- Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA. 2002 Nov 6;288(17):2123-9.
- Lifetime estrogen exposure and cognition in late life: the Cache County Study. Menopause. 2019 Dec;26(12):1366-1374.
- Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology. 2012 Oct 30;79(18):1846-52.
- Nutritional Status is Associated with Faster Cognitive Decline and Worse Functional Impairment in the Progression of Dementia: The Cache County Dementia Progression Study1. J Alzheimers Dis. 2016 Feb 27;52(1):33-42.
-

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ARIZONA STUDY – INSURANCE STUDY ON CLOSE TO 400,000 WOMEN 2021

- In 379,352 women with or without claim records of HT, use of HT was associated with significantly reduced risk for combined NDDs
- Found women on hormone therapy were up to 58% less likely to develop neurodegenerative diseases including Alzheimer's disease, and reduction of risk varied by type and route of hormone therapy and duration of use.
- Formulations containing natural steroids 17β-estradiol and/or progesterone were associated with greater reduction in NDD risk.
- Oral- HT users showed significantly reduced RRs (0.42, 0.41-0.44, $P < 0.001$) for combined NDDs compared to non-HT users.
- The RRs for transdermal-HT users were significantly decreased for all-cause dementia.
- Greatest reduction in risk of NDD, AD, and dementia emerged in patients aged 65 years or older.
- Further, the protective effect of long-term therapy (>1 year) on combined NDDs, AD, PD, and dementia was greater compared to short-term therapy (≤1 year).
- FP;;PW THE SCOENCE
- Association between menopausal hormone therapy and risk of neurodegenerative diseases: Implications for precision hormone therapy. Alzheimers Dement (N Y). 2021 May 13;7(1):e12174.

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33

ARIZONA STUDY

- Women on HRT 79% less likely to develop Alzheimer's
- 77% less likely to get any neurodegenerative disease
- Much more significant for natural steroids
- Less but still for synthetic protection was 50 to 60%
- Analysis of HT formulations indicated that all formulations containing estrogen reduced risk of NDDs.
- A differentiating factor for efficacy of estrogen was the progestin in the formulation.
- Estrogen with natural progesterone (Prometrium) exerted greater reduction in risk for combined NDDs. Estrogen in combination with the synthetic progestin medroxyprogesterone acetate reduced the protective efficacy of estrogen, which is consistent with previous findings.[62,63]

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UNIVERSITY OF AZ AUTHOR'S SAID

A differentiating factor for efficacy of estrogen was the progestin in the formulation. Estrogen with natural progesterone (Prometrium) exerted greater reduction in risk for combined NDDs.

Estrogen in combination with the synthetic progestin medroxyprogesterone acetate reduced the protective efficacy of estrogen, which is consistent with previous findings

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MULTIPLE FACTORS IMPACT BIOLOGICAL AND PHARMACOKINETIC PROPERTIES OF NATURAL VERSUS SYNTHETIC PROGESTINS

- Orally administered progesterone and medroxyprogesterone acetate have different pharmacokinetics including bioavailability and half-life, which could be responsible for different effects of progestins.
- Progesterone and medroxyprogesterone acetate also differ in their chemical structure.
- And their binding affinities to steroid receptors including androgen, glucocorticoid, and mineralocorticoid receptors, which could be related to different risk profiles.
- Moreover, **progesterone stimulates oligodendrocyte and myelin repair in preclinical in vitro and in vivo studies whereas medroxyprogesterone acetate has potential adverse outcomes for neural regeneration**.

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ROUTE OF ADMINISTRATION

- Although the risks of dementia, MS, and all combined NDDs were **significantly reduced in transdermal HT users**.

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- Nonetheless, while diagnosable AD may not be treatable by hormone therapy, its **preceding stage of mild cognitive impairment may very well be treatable by hormone therapy**.
- From Menopause to Neurodegeneration-Molecular Basis and Potential Therapy. Int J Mol Sci. 2021 Aug 11;22(16):8654. doi: 10.3390/ijms22168654. PMID: 34445359; PMCID: PMC8395405.

REDUCE MCI

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ARIZONA STUDY

- Women who underwent menopausal hormone therapy for six years or greater were 79% less likely to develop Alzheimer's and 77% less likely to develop any neurodegenerative disease.
- "This is not the first study on the impact of hormone therapies on neurodegenerative disease reduction," said Roberta Diaz Brinton, PhD, director of the U Arizona Center for Innovation in Brain Science and senior author on the paper.
- "**But what is important about this study is that it advances the use of precision hormone therapies in the prevention of neurodegenerative disease, including Alzheimer's."**

40

- **References:**
- Mindfulness, Exercise Strike Out in Memory Trial - *Medscape* - Dec 13, 2022.
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.
- Sexy Brain Berkson DL Awakened Medicine Press
- The End of Alzheimer's: The First Program to Prevent and Reverse Cognitive Decline, Penguin Random House (2017)
- Effects of Hormone Therapy on survival, cancer, cardiovascular 1 and dementia risks in 7 million menopausal women over age 65: a retrospective observational study. medRxiv preprint doi: https://doi.org/10.1101/2022.05.25.22275595; May 2022.
- Estrogen therapy and cognition: a review of the cholinergic hypothesis. Endocr Rev. 2010 Apr;31(2):224-53. doi: 10.1210/er.2009-0036. Epub 2009 Dec 17. PMID: 20019127; PMCID: PMC2852210.

HRT PRESERVES MEMORIES

41

41

- More than exercise
- More than food
- Rule the brain (hippocampal volume, rule much more than sexy or reproductive things),
- Found in Covid rule CD4+. CD8+, T-reg, on and on.
- **So why all this mystery and distrust?**

HORMONES MOST POWERFUL SIGNALING SYSTEM IN THE BODY

42

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WHY THIS FEAR?

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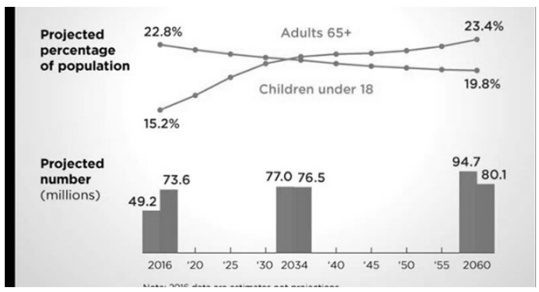

NOT TOPPLE MEDICARE

44

44

JULY
2002

The WHI – what was it?

- Funded by the NIH
- From 1993 to 1998, more than 27,000 postmenopausal women aged 50 to 79 years with no prior breast cancer enrolled in one of two randomized, placebo-controlled WHI trials
- At 40 US centers,
- Women with an intact uterus received CEE (0.625 mg/day) plus MPA (2.5 mg/day) or placebo (n = 8102)
- Women with prior hysterectomy received CEE alone (n = 5310) or placebo (n = 5429) for a median of 7.2 years.
- Prematurely stopped at median 5 years
- July 2002
- Tracked through Dec. 2019

45

- November, months later
- 2022
- It was not taken seriously.

- Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA. 2002 Nov 6;288(17):2123-9.

WHEN DID THE CACHE COUNTY DEMENTIA STUDY COME OUT?

46

!

Litigious Country
Assaulted Hormones, Awareness & Availability

- Physicians
- Patients
- Understandable
- But in US
- Not Europe
- Where given for free in socialized countries like Finland to keep aging women safer and government health programs from toppling

47

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WOW!

Socialized Medicine Countries
HRT - free/easy access

- **Wales and Scotland HRT is free**
- **France = free and/or greatly reduced.**
- **Italy – gives HRT for free to all women + trans.**
- **HRT in England -** HRT prescriptions will be made available on an annual basis, reducing the cost greatly. Much free.
- **Most Nordic countries** give HRT for free
- US is trying to limit source of half the women presently on HRT.

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FINLAND

18 years giving HRT for free to aging women as script

- Breast Cancer Risk in Postmenopausal Women Using Estrogen-Only Therapy
- 112,000 women
- 1994-2001
- Followed for bc with aid of Finnish Cancer registry to 2002

- CONCLUSION: Estradiol for 5 years or more, either orally or transdermally, means 2–3 extra cases of breast cancer per 1,000 women who are followed for 10 years. (Obstet Gynecol 2006; 108:1354–60)
- Oral estradiol use for less than 5 years, oral estriol, or vaginal estrogens were not associated with a risk of breast cancer.
- From the Department of Obstetrics and Gynecology, Helsinki University Central
- Hospital, Helsinki, Finland; and Finnish Cancer Registry, Institute for Statistical
- and Epidemiological Cancer Research, Helsinki, Finland.

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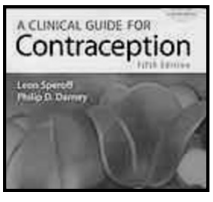
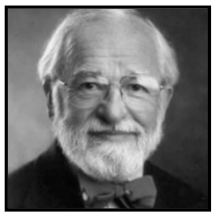
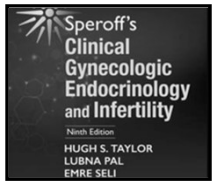
- **Wrote multiple studies urging physicians to not let a singular randomized trial**
- **Stop what decades of clinical outcomes had shown.**

CHAMPIONED PAST CLINICAL OUTCOMES







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HOODIS 2018 REANALYSIS
WHI HORMONE METHODOLOGY WAS FLAWED

- In the WHI, unopposed conjugated equine estrogen (CEE) reduced breast cancer risk and mortality.
- The increased HR was not due to an increased breast cancer incidence rate in women randomized to CEE + MPA therapy but rather
- **Due to a decreased and unexpectedly low breast cancer rate in the subgroup of women with prior HT use randomized to placebo**.
- **Why? Forgot to control for PAST USE OF ERT in CONTROL GROUP.**
- **Any association that may exist between HT and breast cancer appears to be rare and no greater than other medications commonly used in clinical medicine.**

Menopausal hormone therapy and breast cancer: what is the evidence from randomized trials? Climacteric. 2018 Dec;21(6):521-528. doi: 10.1080/13697137.2018.1514008. Epub 2018 Oct 9. PMID: 30296850; PMCID: PMC6386596.

51

51

19-YEAR RE-ANALYSIS WHI

ESTROGEN ONLY: CEE

- **Significant 23% reduction in breast cancer**
- **If get breast cancer, fatality 44% reduction with CEE**

Efects continue for up to 20

= DR. ABRAHAM MORGENTALER FINDING SAME THING IN MALES WITH T.

- --San Antonio Breast Cancer Symposium 2019: Abstract GS5-00. Presented December 13, 2019.
- --Medscape Medical Oncology, Dec. 13, 2019

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IN HEALTHY WOMEN

- Estrogen protects breast against breast cancer.
- Estrogen protects women from dying if they get breast cancer.
- Same with males.
- Testosterone protects against getting prostate cancer, especially very aggressive kind, and dying from it if you do get it.

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WHI RE-ANALYSIS AUTHORS

- **The Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA;**
- **Fred Hutchinson Cancer Research Center, Seattle, WA;**
- **Brigham and Women's Hospital, Boston, MA;**
- **Stanford Prevention Research Center, Stanford, CA;**
- **University of Washington, Seattle, WA;**
- **Pitt Public Health, Pittsburgh, PA;**
- **Karmanos Cancer Institute, Detroit, MI;**
- **Stony Brook University, Stony Brook, NY;**
- **University of Tennessee Health Science Center, Memphis, TN;**
- **Albert Einstein Cancer Center, Bronx, NY;**
- **The Ohio State University, Columbus, OH, and**
- **The UF Health Internal Medicine, Gainesville, FL.**

- 2019 SABCS Abstracts Home GS5-00. Long-term influence of estrogen plus progestin and estrogen alone use on breast cancer incidence: The Women's Health Initiative randomized trials.

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RANDOMIZED ISSUES

- **Randomized Controlled Trials (RCTs) are increasingly popular in the social sciences, not only in medicine.**
- **We argue that the lay public, and sometimes researchers, put too much trust in RCTs over other methods of investigation.**
- **Contrary to frequent claims in the applied literature, randomization does *not* equalize everything other than the treatment in the treatment and control groups, it does not automatically deliver a precise estimate of the average treatment effect commonly believed.**
- **A best, an RCT yields an unbiased estimate, but this property is of limited practical value.**

- **Understanding and misunderstanding randomized controlled trials Soc Sci Med. 2018 Aug; 210: 2–21. Published online 2017 Dec 25. doi: 10.1016/j.socscimed.2017.12.005**
- **PMCID: PMC6019115m NIHMSID: NIHMS930764 PMID: 29331519**

- **Princeton University, USA; National Bureau of Economic Research, USA; University of Southern California, USA. Electronic address: deaton@princeton.edu.**
- **[2]Durham University, England; UC San Diego, USA.**

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RE-ANALYSES OF RANDOMIZED TRIAL DATA - ALMOST 35% GAVE DIFFERENT OUTCOMES/CLINICAL DIRECTION

- **Results** We identified 37 eligible reanalyses in 36 published articles, 5 of which were performed by entirely independent authors
- Reanalyses differed most commonly in statistical or analytical approaches (n = 18) and in definitions or measurements of the outcome of interest (n = 12).
- Four reanalyses changed the direction and 2 changed the magnitude of treatment effect, whereas 4 led to changes in statistical significance of findings.
- **Conclusions and Relevance**
- A small number of reanalyses of RCTs have been published to date.
- Only a few were conducted by entirely independent authors.
- **35% percent of published re-analyses led to changes in findings that implied conclusions different from those of the original article about the types and number of patients who should be treated**.
- **Reanalyses of Randomized Clinical Trial Data** *JAMA*. 2014;312(10):1024-1032. doi:10.1001/jama.2014.9646

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AUTHORS

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WE ONLY LISTEN TO RANDOMIZED TRIALS WHEN WE WANT TO, OR PHARMA WANTS US TO…

WHI cholesterol in older women

- **Design:** Prospective cohort. 68,000.
- **Participants:** Women aged 68 to 81 years at baseline.
- **Measurements:** Serum high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were collected at baseline. Participant survival status and self-reported mobility was compared across lipid levels.
- **Results:**
- intact mobility after adjustment for other cardiovascular risk factors. Compared with the lowest LDL quartile, **the three upper LDL quartiles were associated with greater odds of survival to age 90 with intact mobility** (LDL: Q2 OR = 1.31 [95% CI = .99-1.74]; Q3 OR = 1.43 [95% CI = 1.07-1.92]; Q4 OR = 1.35 [95% CI = 1.01-1.80]; P = .05).
- **Conclusion:** Neither higher HDL nor lower LDL levels predicted survival to age 90, **but higher LDL predicted healthy survival.**
- **These findings suggest the need for reevaluation of healthy LDL levels in older women.**

- Am Geriatr Soc 2020 Feb;68(2):288-296. doi: 10.1111/jgs.16306. Epub 2020 Jan 13. **Associations between Serum Levels of Cholesterol and Survival to Age 90 in Postmenopausal Women**

58

JOINT PAIN

- **Methods:** A total of 10,739 postmenopausal women who have had a hysterectomy were randomized to receive daily oral conjugated equine estrogens (0.625 mg/d) or a matching placebo.
- The frequency and severity of joint pain and joint swelling were assessed by questionnaire in all participants at entry and on year 1, and in a 9.9% random subsample (n = 1,062) after years 3 and 6. Logistic regression models were used to compare the frequency and severity of symptoms by randomization group. Sensitivity analyses evaluated adherence influence on symptoms.
- **Results:** At baseline, joint pain and joint swelling were closely comparable in the randomization groups (about 77% with joint pain and 40% with joint swelling).
- After 1 year, joint pain frequency was significantly lower in the estrogen-alone group compared with the placebo group (76.3% vs 79.2%, P = 0.001), as was joint pain severity, and the difference in pain between randomization groups persisted through year 3.
- However, joint swelling frequency was higher in the estrogen-alone group (42.1% vs 39.7%, P = 0.02). Adherence-adjusted analyses strengthen estrogen's association with reduced joint pain but attenuate estrogen's association with increased joint swelling.
- **Conclusions:** The current findings suggest that estrogen-alone use in postmenopausal women results in a modest but sustained reduction in the frequency of joint pain.
- Menopause. 2018 Nov;25(11):1313-1320. doi: 10.1097/GME.0000000000001235. **Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial**

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JOINT PAIN

- Receptor Detox – allow body/joints bioavailability of hormones
- Hormone Balance & Protect – sustain levels throughout the day and reduce swelling
- BHRT joint pain
- Experience of hormone MD
- ND lecturer ICIM
- Niacinamide (William Kaufman First Century Prolonged Release Niacinamide two 500 mg BID) joint swelling

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NIH 7 MILLION ESTROGEN STUDY

- **Effects of Hormone Therapy on survival, cancer, cardiovascular and dementia risks in 7 million menopausal women over age 65: a retrospective observational study**
- **Largest study ever run on efficacy, safety of hormones, especially in Medicare age.**

- **doi:** https://doi.org/10.1101/2022.05.25.22275595
- **This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.**
- **Yale BMJ Preprints**

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METHODS

- From 2007-2019 enrollment records of 100% Medicare beneficiaries, we identified 7 million female enrollees aged 65 or more.
- We identified type, route and strength of estrogen based on their prescription drug utilization records.
- Using vital status record and encounter records, we defined the first onset of thirteen patient outcomes; all-cause mortality;
- 5 cancers (breast, lung, endometrial, colorectal, ovarian cancers);
- CV conditions (ischemic heart diseases, heart failure, venous thromboembolism, stroke, atrial fibrillation, acute myocardial infarction);
- And dementia.
- Then, we implemented an extended Cox regression analysis to examine the effects of type, route, and strength of estrogens on each of 13 study outcomes.

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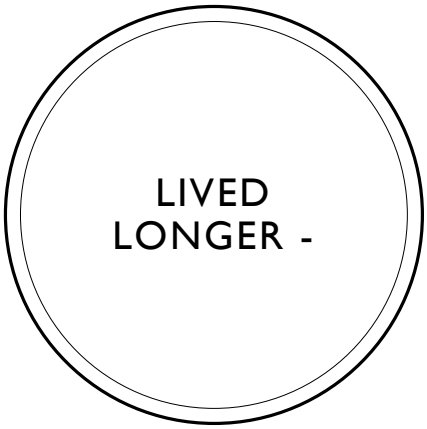

- On average, ET use was associated with a significant, 20% reduction in mortality risk relative to no ET use, which translated to 77,401 fewer expected deaths in our large population.
- All combinations of ET type, route, and dose were also associated with reduced mortality risk.
- **Oral CEE medium dose, comparable to the drug in the WHI trial of ET, exhibited less** risk reduction in mortality (9%) than overall ET.

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- In our study, **vaginal E_2 in low and medium doses were associated with greatest reduction of mortality** risk.
- Our overall **mortality results are consistent with the mortality results from a meta-analysis of 31 observational and RCT studies** that reported reduced mortality among HT users (34) and with the re-analyses of the Prostate, Lung, Colorectal, and
- Ovarian (PLCO) Cancer Screening RTC, which reported a 23% decrease in all-cause mortality among current users of any HT (35).

64

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CITATIONS

- 34. The impact of menopausal hormone therapy on overall mortality a comprehensive review. https://doi.org/101080/1369713720201767568 [Internet]. 2020 Sep 2 [cited 2022 Apr 11];23(5):447–59. Available from:
- https://www.tandfonline.com/doi/abs/10.1080/13697137.2020.1767568
- 35. Hormone Replacement Therapy and Colorectal Cancer Incidence and Mortality in the Prostate, Lung, Colorectal, and Ovarian Cancer
- Screening Trial. Clin Colorectal Cancer. 2018 Jun 1;17(2):e281–8.

65

ABSTRACT HIGH RISK CARDIAC PATIENTS HAD BEST LONGEVITY OUTCOMES NOT WORSE

- Menopausal hormone therapy (MHT) is indicated for menopausal symptom relief. However, MHT has also been shown to be beneficial for prevention of long-term estrogen deficiency sequelae **including mortality.**
- Based on a comprehensive literature review (**meta-analysis of 31 observational studies)** on MHT and mortality, the authors' recommendations are as follows:
- in postmenopausal women, MHT appears to confer a **(significant) reduction in overall mortality;** the benefit especially applies to women who initiate **long-term** MHT early after menopause;
- **in women with prevalent cardiovascular risk factors (except for diabetes mellitus, where results are mixed), the benefit of MHT on overall mortality is even more pronounced;** and, however, study results are difficult to compare due to heterogeneous study designs.
- The impact of menopausal hormone therapy on overall mortality - a comprehensive review. Climacteric. 2020 Oct;23(5):447-459. doi: 10.1080/13697137.2020.1767568. Epub 2020 Jun 18. PMID: 32552066.

66

FINDINGS

- Effects of Hormone Therapy on survival, cancer, cardiovascular, and dementia risks

- **Estrogen monotherapy (ET) exhibited a significant, 20%, relative risk reduction of mortality.**
- **The reduction was greater with estradiol (than conjugated estrogen (aHR=0.86; 95% CI 0.85-0.88), and with vaginal.**
- **Less with oral better with transdermal.**
- **ET also exhibited significant risk reductions for all study cancers, breast, ovary, lung, uterus, colon**
- **ET slightly increased risks of ischemic heart diseases if oral.**
- **However, such risk was not observed with low dose ET or transdermal.**
- **Both combination therapy and progestogen monotherapy, progestins, exhibited a significantly increased risk of breast cancer.**
- **Oral HT exhibited a moderately increased risk of dementia.**

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BEJUVA IS THE ONE BHRT THAT IS FDA APPROVED AND IT IS ORAL

- BIJUVA® is the FIRST AND ONLY FDA-approved combination of bio-identical estradiol and bio-identical progesterone in a single daily oral capsule. BIJUVA is proven to reduce moderate to severe hot flashes while reducing risk to the lining of the uterus.
- Use to be called Replenish.

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BIOIDENTICAL

- A combined, bioidentical, oral, 17β-estradiol and progesterone capsule for the treatment of moderate to severe vasomotor symptoms due to menopause. Expert Rev Clin Pharmacol. 2019 Aug;12(8):729-739. doi: 10.1080/17512433.2019.1637731. Epub 2019 Jul 22. PMID: 31282768.
- **Expert opinion**: In REPLENISH (NCT01942668), the two highest doses of TX-001HR significantly reduced VMS frequency and severity at 4 and 12 weeks versus placebo (co-primary endpoints); all doses met the primary endpoint of endometrial safety. Rates of amenorrhea were high and improved over time; the Menopause Quality of Life and Medical Outcomes Study-Sleep instruments improved with E2/P4. TX-001HR was well tolerated and had no clinically significant impact on vital signs, metabolic or coagulation parameters, or breast safety. The combination bioidentical E2/P4 capsule (1 mg/100 mg dose was FDA-approved as Bijuva in October 2018) may provide a safe, effective, rigorously studied alternative for women with a uterus who prefer CHT for relief of VMS.
- **elevance to patient care and practice:** Concerns over content and safety of compounded bioidentical hormones have been raised by several professional societies. As women experience VMS of menopause, a desire for a Food and Drug Administration-regulated bioidentical combination product for the treatment of moderate to severe menopausal symptoms may be desirable. Given as a once-daily oral capsule at the dose of 1 mg estradiol/100 mg progesterone, 17β-E/P is approved for the treatment of VMS associated with menopause.
- **Conclusions:** 17β-E/P is a novel bioidentical product that is the first of its kind in the treatment of moderate to severe menopausal symptoms.
- **Bioidentical Oral 17β-Estradiol and Progesterone for the Treatment of Moderate to Severe Vasomotor Symptoms of Menopause**

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THERAPEUTICS MD

- **Objective:** To evaluate the effect of a single-capsule, bioidentical 17β-estradiol (E2) and progesterone (P4) hormone therapy on mammograms and breasts in postmenopausal women after 1 year of use.
- **Methods:** In the 12-month, phase 3, randomized, double-blind, placebo-controlled, multicenter REPLENISH trial, postmenopausal women (40-65 y) with moderate to severe vasomotor symptoms and a uterus were randomized to four active daily dose groups of E2/P4 (TX-001HR) or a placebo group. Mammograms were performed and read locally at screening (or ≤6 months before first dose) and at study end using BI-RADS classification. Incidence of abnormal mammograms and breast adverse events was evaluated.
- **Results:** All but 8 (0.4%) mammograms at screening were normal (BI-RADS 1 or 2). At 1 year, 39 (2.9%) of the 1,340 study-end mammograms were abnormal (BI-RADS 3 or 4); incidence was 1.7% to3.7% with active doses and 3.1% with placebo. Breast cancer incidence was 0.36% with active doses and 0% with placebo. Breast tenderness was reported at frequencies of 2.4% to 10.8% with active doses versus 0.7% with placebo, and led to eight study discontinuations (1.6% of discontinuations in active groups).
- **Conclusions:** In this phase 3 trial of a combined E2/P4, results of secondary outcomes suggest that E2/P4 may not be associated with increased risk of abnormal mammograms versus placebo, and the incidence of breast tenderness was low relative to most of the rates reported in other studies using hormone therapy.
- Breast effects of oral, combined 17β-estradiol, and progesterone capsules in menopausal women: a randomized controlled trial. Menopause. 2020 Dec;27(12):1388-1395. doi: 10.1097/GME.0000000000001631. PMID: 32842052; PMCID: PMC7709925.

70

AUTHORS

- University Hospitals Cleveland Medical Center, Cleveland, OH.
- [2]University of Manitoba, Winnipeg MB, Canada.
- [3]Ms.Medicine, Cincinnati, OH.
- [4]TherapeuticsMD, Boca Raton, FL. (Old CEOs of Prempro originally)
- So when first WHI gave every fear, they turned to making bioidentical hormones.
- But oral.
- Which all research shows has the most issues from coagulation to stroke.

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ESTRADIOL VS. PREMARIN (CONJUGATED EQUINE ESTROGEN)

- Estradiol protected anti-aging or longevity twice as good as Premarin, but both protected.
- Premarin protected against breast cancer twice as good as estradiol, but both protected.
- Arizona University outcomes on cognition both protected, but bioidentical or natural steroids protected brain health best.

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NOT SAID IN ABSTRACT - ORAL

- **Overall ET use had small or no, associations with, stroke or dementia, risk.**
- **However, high and medium doses of oral E2 and CEE had important increased risk of stroke, breaching 25% with high dose oral CEE.**
- **Both estrogen types (CEE and E2) were also associated with increased dementia risk but only with high dose oral preparations.**
- **Transdermal and vaginal preparations of ET, that avoid first pass travel through the liver were associated with small reduced or null risk of both conditions, consistent with the results of other studies and with the procoagulant and proinflammation effects of estrogen's liver passage**
- **EPT use, on average, was also associated with small but significant, increased risk of dementia and, decreased risk of all 6 CV conditions.**

- **Oral vs transdermal estrogen therapy and vascular events: A systematic review and meta-analysis. J**
- **Clin Endocrinol Metab [Internet]. 2015 Nov 1 [cited 2022 Mar 29];100(11):4012–20. Available from: https://academic.oup.com/jcem/article/100/11/4012/2836071**

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APOE4- HRT INCREASES BRAIN VOLUME

- The study shows that HRT use is associated with better memory, cognition and larger brain volumes in later life among women carrying the APOE4 gene -- the strongest risk factor gene for Alzheimer's disease.
- The research team found that HRT was most effective when introduced early in the menopause journey during **perimenopause**.
- Prof Anne-Marie Minihane, from UEA's Norwich Medical School and director of the Norwich Institute for Healthy Aging at UEA, led the study in collaboration with Prof Craig Ritchie at the University of Edinburgh.
- Prof Minihane said: "We know that 25 per cent of women in the UK are carriers of the APOE4 gene and that almost two thirds of Alzheimer's patients are women.
- "In addition to living longer, the reason behind the higher female prevalence is thought to be related to the effects of menopause and the impact of the APOE4 genetic risk factor being greater in women.
- **Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort**. *Alzheimer's Research & Therapy*, 2023; 15 (1) DOI: 10.1186/s13195-022-01121-5 Norwich Medical School
- Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

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STUDY CAME OUT JAN 2023

- The research team studied data from 1,178 women participating in the European Prevention of Alzheimer's Dementia initiative -- which was set up to study participants' brain health over time.
- The project spanned 10 countries and tracked participants' brains from 'healthy' to a diagnosis of dementia in some. Participants were included if they were over 50 and dementia-free.
- The research team studied their results to analyse the impact of HRT on women carrying the *APOE4* genotype.
- Dr Rasha Saleh, also from UEA's Norwich Medical School, said: "We found that HRT use is associated with better memory and larger brain volumes among at-risk APOE4 gene carriers. The associations were particularly evident when HRT was introduced early -- during the transition to menopause, known as perimenopause.
- "This is really important because there have been very limited drug options for Alzheimer's disease for 20 years and there is an urgent need for new treatments.
- "The effects of HRT in this observation study, if confirmed in an intervention trial, would equate to a brain age that is several years younger."

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HRT

- Protects against APOE4 Alzheimer's vulnerability gene
- Best started early
- Enlarges brain volume
- Can be used in older women and even high risk cardiac women.
- SIZE matters
- But question of cancer
- Question of coagulation
- Question of Milestones of Reproduction and age of lowering hormones – game changing.

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ESTROGEN ENHANCES HIPPOCAMPAL GRAY MATTER VOLUME IN YOUNG AND OLDER POSTMENOPAUSAL WOMEN: A PROSPECTIVE DOSE RESPONSE STUDY

- [1]The Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN
- [2]Clinical Neuroscience Research Unit, Department of Psychiatry, University of Vermont College of Medicine, Burlington, VT
- [3]The Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN
- **Address for correspondence:** Paul Newhouse, M.D. Vanderbilt Center for Cognitive Medicine, Department of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Ave. South, Nashville, TN 37212, V: 615-327-7030, F: 615-875-0686, ude.tlibrednaV@esuohweN.luaP

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AMOUNT OF ESTROGEN MATTERS FOR BRAIN PROTECTION

- Estrogen administration following menopause has been shown to support hippocampally-mediated cognitive processes. A number of previous studies have examined the effect of estrogen on hippocampal structure to determine the mechanism underlying estrogen effects on hippocampal function. However, these studies have been largely observational and provided inconsistent results.
- We examined the effect of short-term estradiol administration on hippocampal gray matter volume in a prospective study with multiple doses of estradiol (placebo, 1 mg, and 2 mg).
- Following three months of estradiol administration bilateral posterior hippocampal voxel-based **gray matter volume was increased in women who received 2 mg estradiol**.
- There were no significant differences in total hippocampal volume and no significant effects on gray matter volume in women who received placebo or 1 mg estradiol. These findings accord with previous animal studies and provide evidence of estrogen effects on hippocampal morphology that may represent a neurobiological mechanism for estrogen effects on cognition in post-menopausal women.
- Estrogen enhances hippocampal gray-matter volume in young and older postmenopausal women: a prospective dose-response study. Neurobiol Aging. 2017 Aug;56:1-6. doi: 10.1016/j.neurobiolaging.2017.03.033. Epub 2017 Apr 8. PMID: 28478324; PMCID: PMC5875178.

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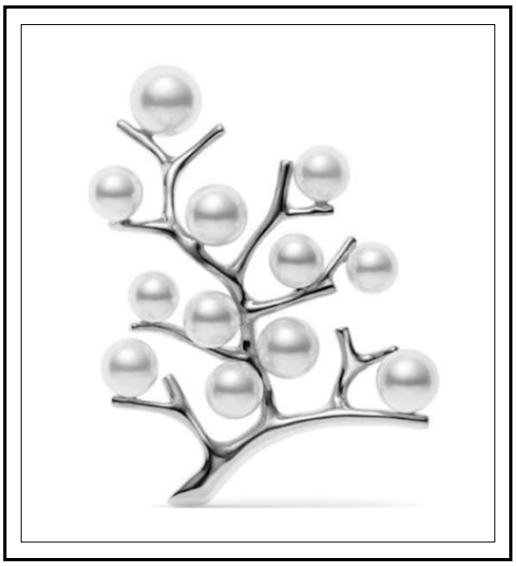
DOSING PEARLS

- Be guided by how they feel
- Breast nipple tenderness, give 3 days for acclimation
- If sustained, decrease E and or increase P
- Bleeding issues usually mean too little P or too much E
- Or hormone holidays, which do not work for all or perhaps most
- Start at .25 mg of E2 .75 mg of E3 and slowly taper up
- Average woman usually needs between .8 to 2.6 estradiol equivalents
- E3 is 1/8th the potency approximately of E2



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FSH LEVELS WHEN HRT IS OPTIMAL

Women – <20 mIU/mL in women

Males 4.5 **– 7.5- 12 mIU/mL (work in progress)**

Redefining abnormal follicle-stimulating hormone in the male infertility population. BJU Int. 2012 Aug;110(4):568-72. doi: 10.1111/j.1464-410X.2011.10783.x. Epub 2011 Dec 16. PMID: 22177092.

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