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MD MSc BSc

Clinical Endocrinology: Safety & Efficacy of BHRT in a Clinical Setting

Henri Knafo, MD

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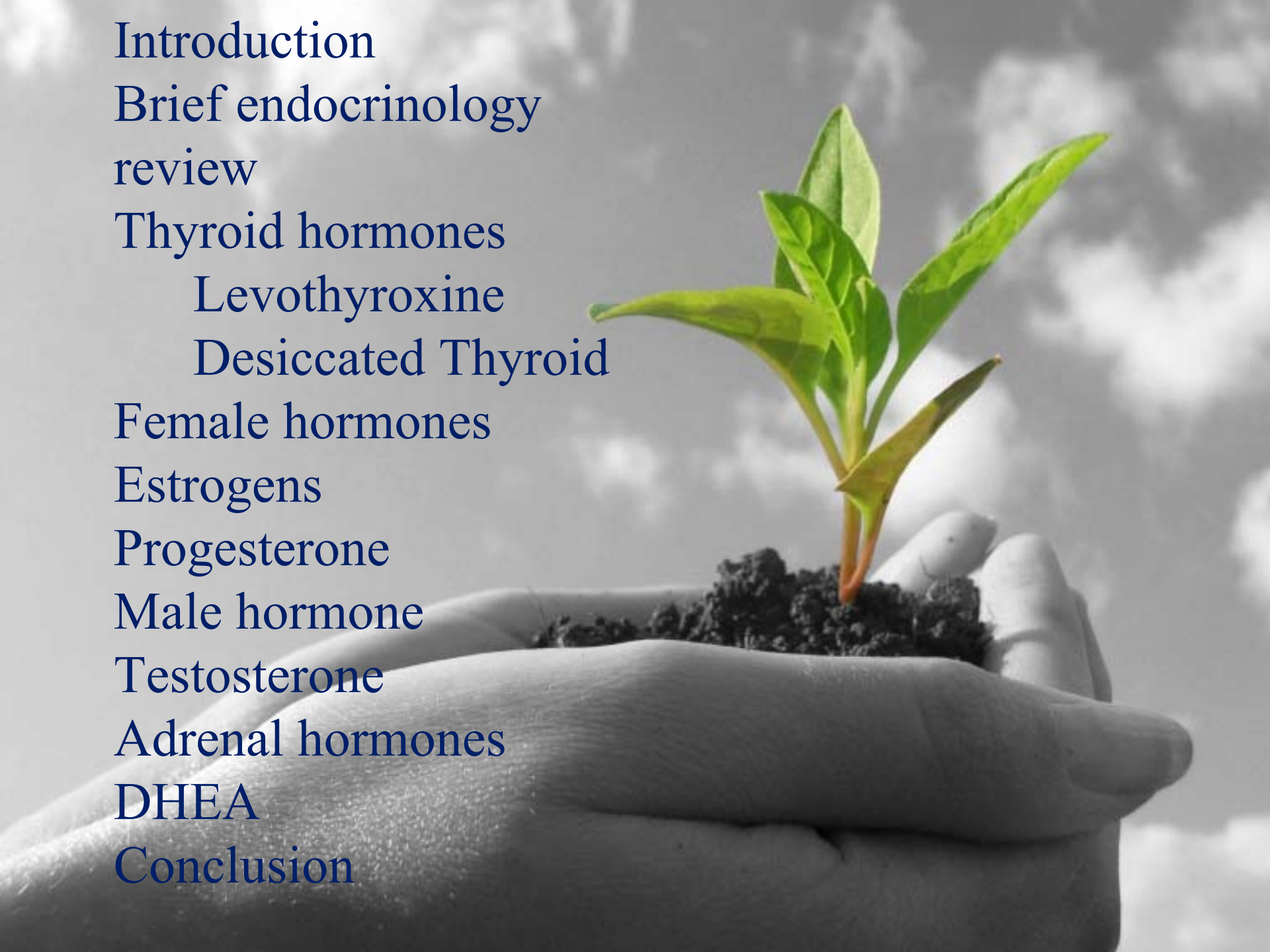
Abstract

Henri Knafo MSc. MD

Dr. Henri Knafo is presently the Medical Director of ERFA Canada the only licensed provider of natural desiccated thyroid in Canada. He has given numerous conferences around the globe on anti-ageing. Dr Knafo was trained first as a Biologist in Montreal (Quebec) where he obtained his Master's in Biomedical Research. He then got his MD at Semmelweis Medical School in Budapest, (Hungary) just before returning to Canada where he trained as a Neurosurgical resident for 5 years. His lecture will focus on clinical endocrinology with an emphasis on bio-identical hormones, safety, efficacy and using them in a clinical setting.

Disclaimer

- The information and reference materials contained herein are intended solely to provide background information.
- They were written for an audience of physicians (MD and NP) as participants of this conference.
- The speaker is in no way payed additional money by any pharmaceutical companies mentioned in this presentation.
- The speaker is working as a medical director for ERFA Canada 2012 Inc. but does not receive additional money or additional compensation for this presentation.



- Introduction
- Brief endocrinology review
- Thyroid hormones
  - Levothyroxine
  - Desiccated Thyroid
- Female hormones
- Estrogens
- Progesterone
- Male hormone
- Testosterone
- Adrenal hormones
- DHEA
- Conclusion

Introduction

What will you learn in this presentation?

- Identify patients that need BHRT.
- Define a proper treatment protocol for these patients.
- Inform the patient about possible side effects of the medication.
- Know what to do if a side effect occurs

INTRODUCTION

• What is BHRT?

- ✓ Replacing hormones that are identical, on a molecular level, with endogenous hormones in our body.
- ✓ Hormones come from plants, animals or are chemically synthesized.
- ✓ Bioidentical hormones are medications
- ✓ Like any medication they can have short term and long term side effects

Historical perspective

AD 1025 Chinese extracted sex hormones from human urine (ch'iu shih)

1930 James Collip developed a method to extract an orally-active estrogen from the urine of pregnant women (Emmenin)

1941 Premarin easily-manufactured conjugated equine estrogens – Not Bioidentical

1998 the FDA approved Prometrium an oral bioidentical progesterone

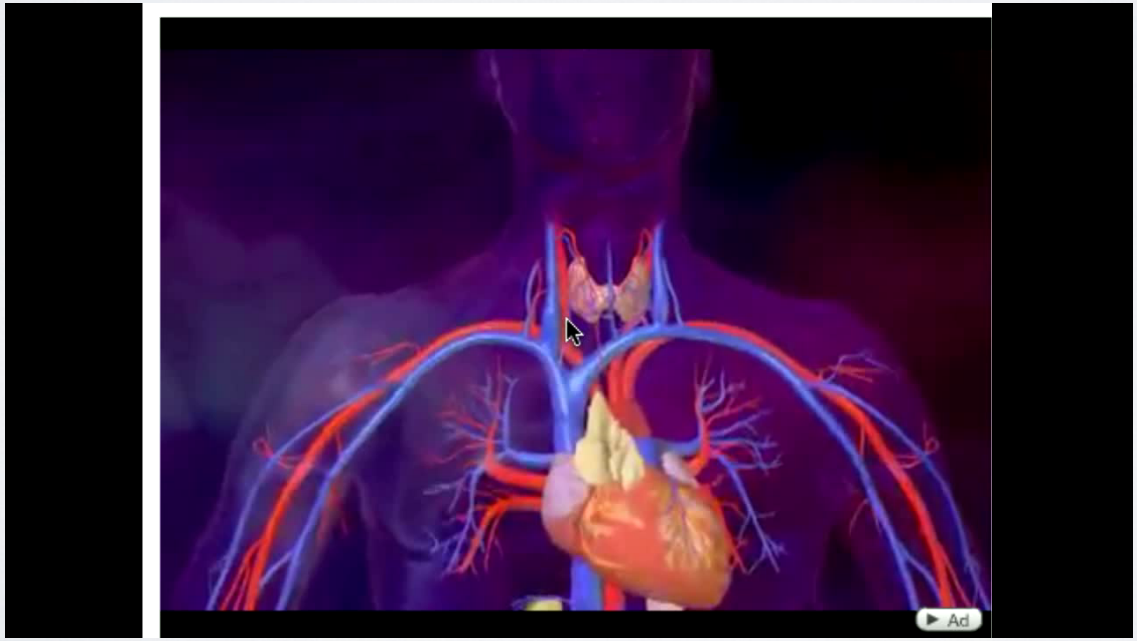
J.B Collip in his office at McGill University Ca. 1930

PHARMACOVIGILANCE

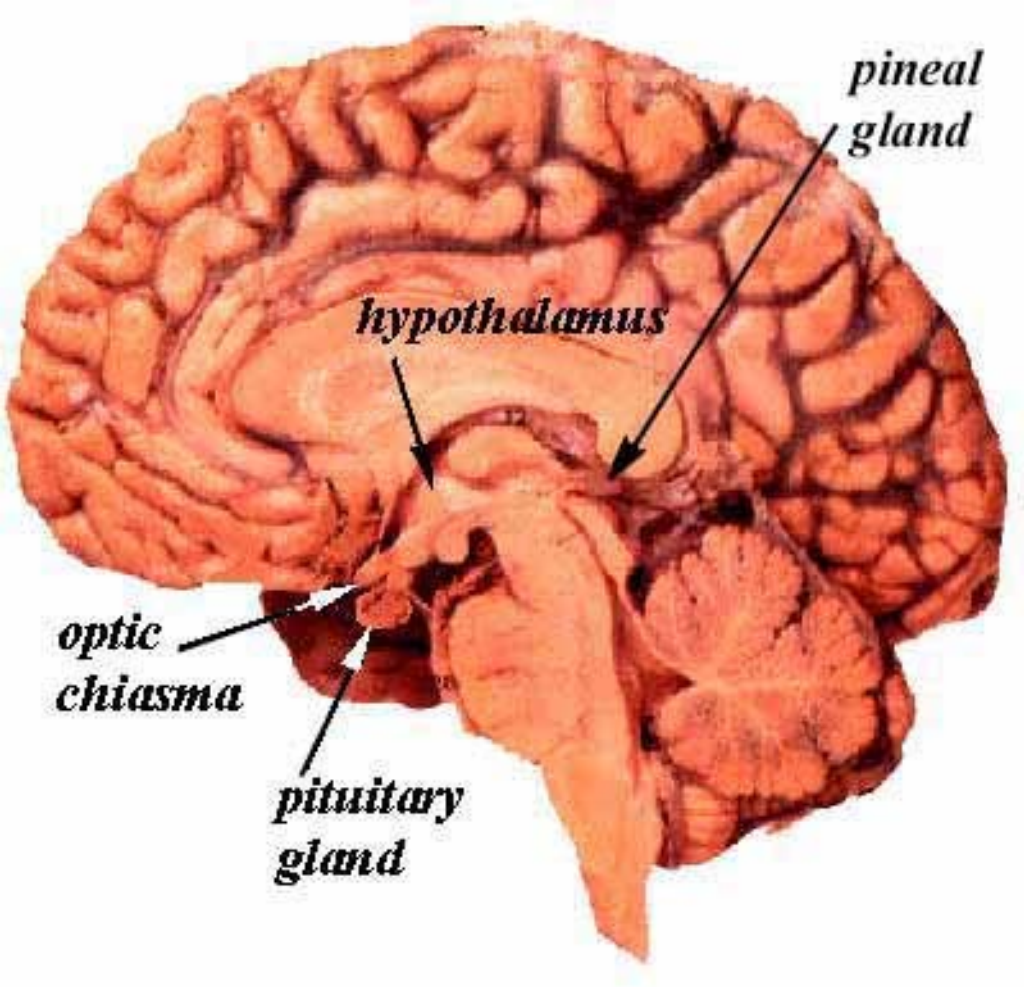
- Product monograph – Read it!
- Side effect reporting mechanism in the world
- Health Canada/Europeen adverse reaction database
- Pubmed

Brief Endocrinology review

- Consists of discrete individual glands that produce and secrete chemical messengers known as hormones.
- Hormones travel from endocrine organs to their targets via the blood.
- Target cells are cells that have receptors for specific hormones on them.



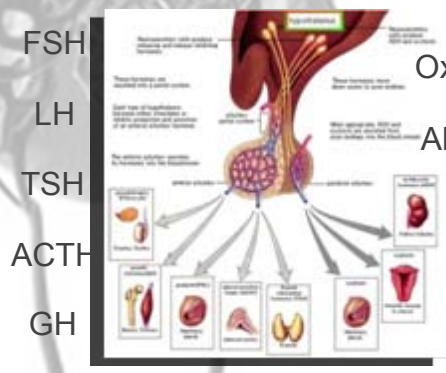
Brief Endocrinology review



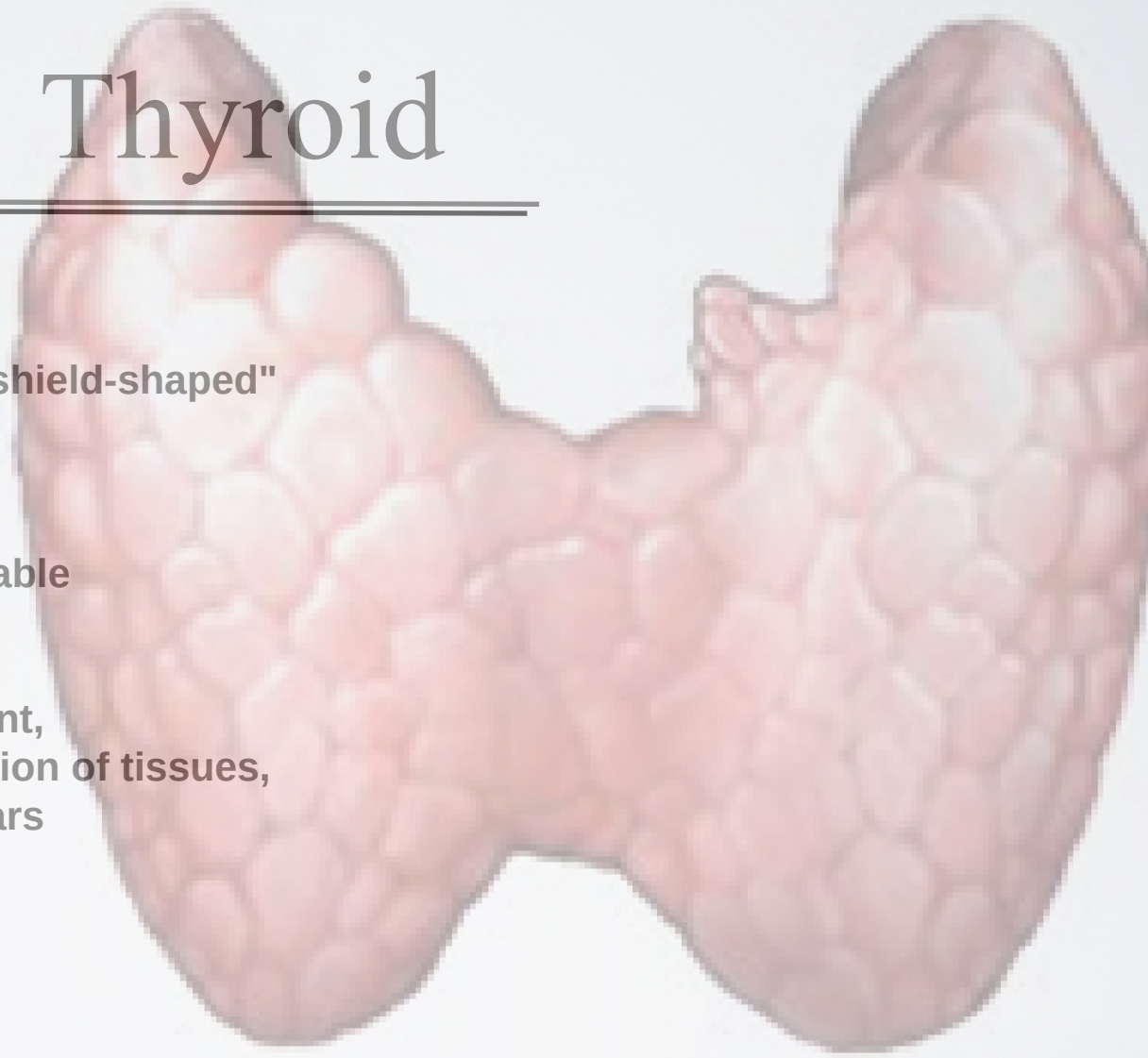
Brief Endocrinology review

The Six Major Anterior pituitary hormones are:

1. Thyroid Stimulating Hormone (TSH or thyrotropin)
2. Follicle Stimulating Hormone (FSH, a gonadotropin)
3. Luteinizing Hormone (LH, a gonadotropin)
4. Adrenocorticotropic Hormone (ACTH, or corticotropin)
5. Growth Hormone (GH)
6. Prolactin (PRL)



Thyroid



Thyroid gland

- **Greek "thyreoeides", meaning "shield-shaped"**
- **Front of neck**
- **A butterfly**
- **Measuring approximately 4 cm**
- **It is normally not, or barely palpable**

- **Secretes hormones**
- **bone growth, mental development,**
- **stimulation of oxygen consumption of tissues,**
- **transformations of fats and sugars**

Secretes T3 and T4

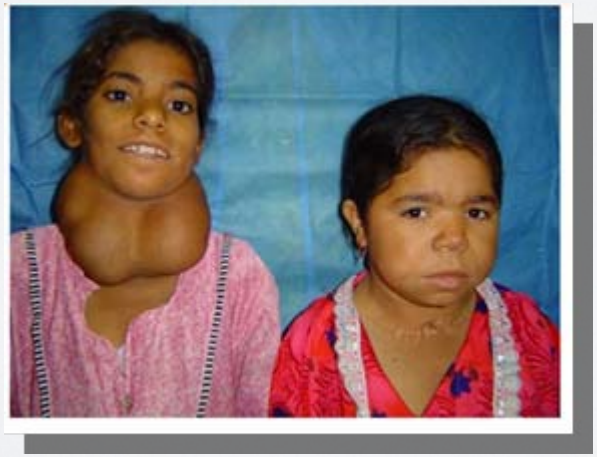
Thyroid

Primary hypothyroidism - It comes from the gland
chronic iodine deficiency;
autoimmune thyroiditis (Hashimoto's thyroiditis)
infiltrative disease (sarcoidosis, amyloidosis, hemochromatosis ...)
enzymatic disorder of the thyroid (genetics)
Congenital thyroid dysgenesis

Secondary hypothyroidism comes from the brain
hypopituitarism
Hypothalamic lesion
TRH deficiency

HypoThyroid

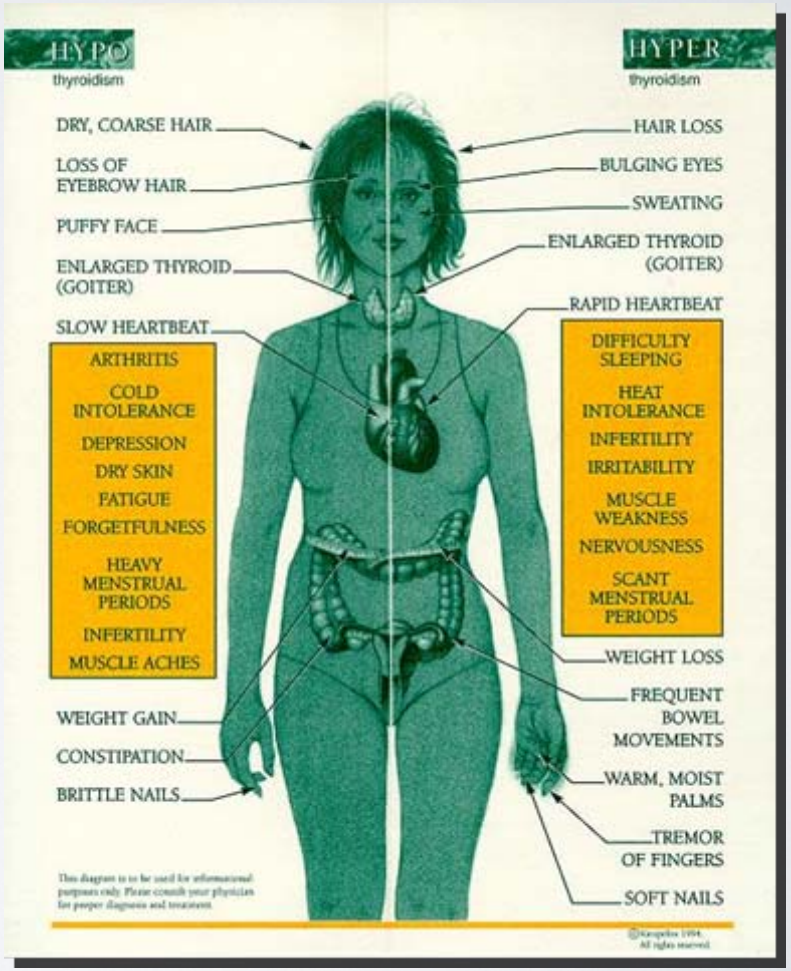
- Frequency 3.6% of the population
More common in women thin
- More common in the elderly -
    5.9% of women> 60 years
    2.4% of men> 60 years
- The most common cause worldwide - iodine deficiency
- Mortality unusual



HypoThyroidism

Symptoms of Hypothyroidism

- Fatigue
- Weakness
- Weight gain or increased difficulty losing weight
- Coarse, dry hair
- Dry, rough pale skin
- Hair loss
- Cold intolerance (you can't tolerate cold temperatures)
- Muscle cramps and frequent muscle aches
- Constipation
- Depression
- Irritability
- Memory loss
- Abnormal menstrual cycles
- Decreased libido



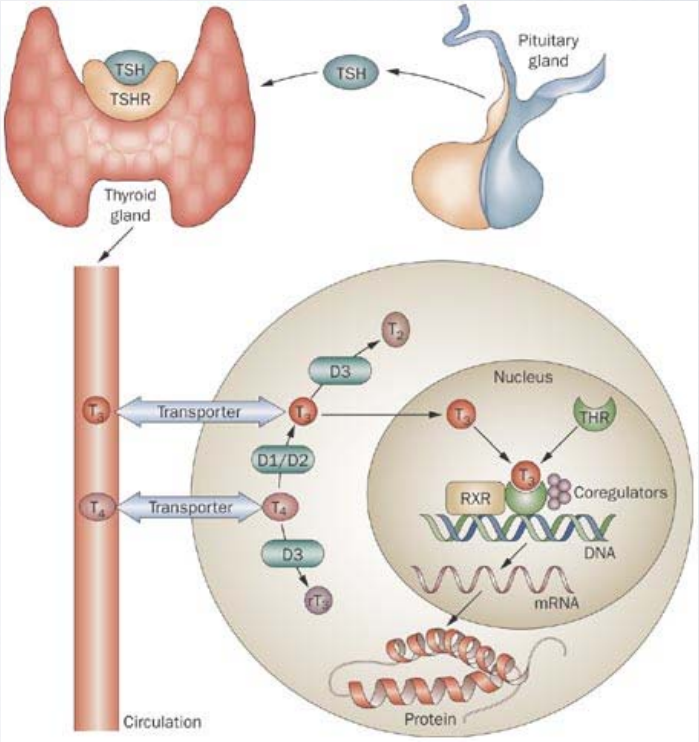
HypoThyroidism

Indication of Hormone replacement

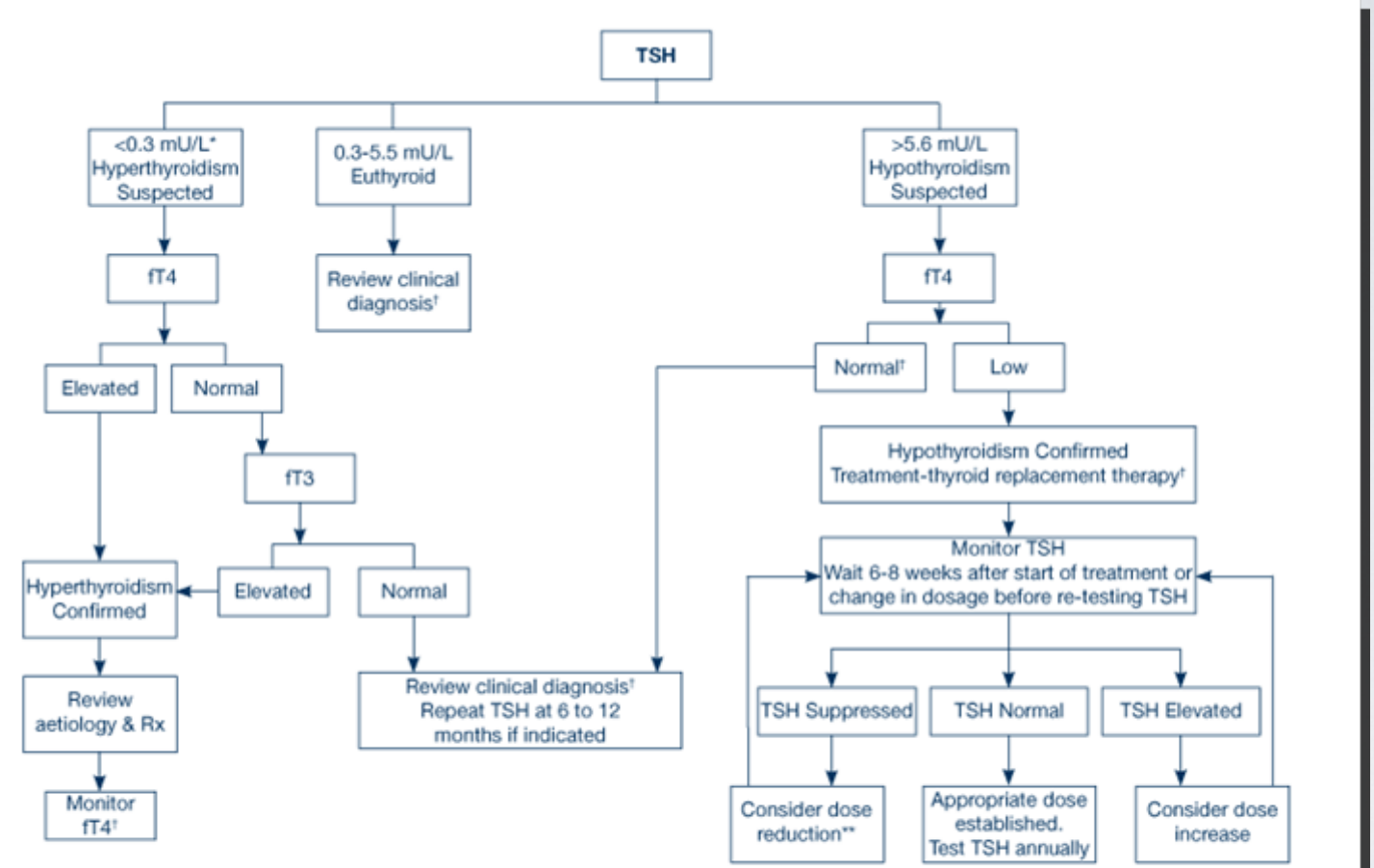
Hypothyrodism

Contraindication

Adrenocortical insufficiency
Thyrotoxicosis
Hypersensitivity
Heart disease (uncontrolled)



Protocole



* Patients with thyrotoxicosis usually have a TSH value of <0.1 mU/L.

** Excess replacement does increase the risk of osteoporosis and arrhythmias, especially in elderly subjects.

† Immunoassays for thyroid function tests are subject to analytical interference due to heterophile antibodies, TSH isoforms, or preanalytic factors.

Hypothyroidism

Standard Treatment

Levothyroxine
ELTROXIN
EUTHYROX
SYNTHROID

T3
CYTOMEL TAB

Desiccated Thyroid
THYROID

Table II – Thyroid® – Conversion Table

Dose of Thyroglobulin (grain)	Equivalents mg	Dose of Desiccated Thyroid (grain)	Dose of T4 (levo thyroxine) mg	Dose of T3 (lio thyronine) µg
0.5	32	0.5	0.05	12.5
1	65	1	0.1	25
2	130	2	0.2	50
3	200	3	0.3	75
4	260	4	0.4	100
5	325	5	0.5	125

Narrow therapeutic window

Desiccated Thyroid

Porcine thyroid glands, dried and powdered for therapeutic use

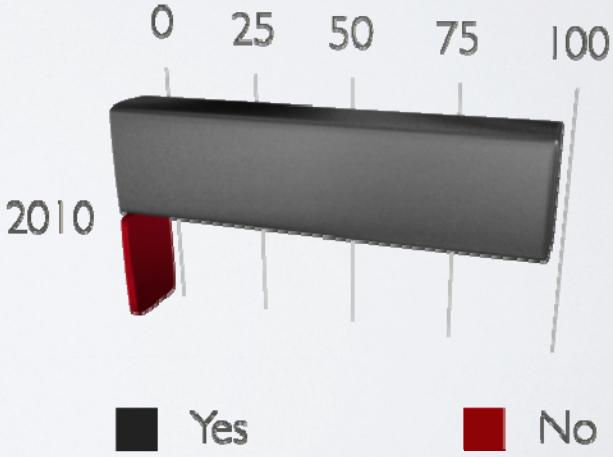
Developed in the late 19th century

Contains a mix of T4 (thyroxine), T3 (triiodothyronine) in the proportions usuallypresent in pig thyroids (approximately 80% T4 and 20% T3).

Use to have inconsistent dosages. There is no more then 10% variation from batch to batch nowadays

Available in 30mg, 60mg, 125mg

Did you feel a positive difference when switching from Leothyroxine to Thyroid ?



Safety

Health Canada adverse reaction report

Very few side effects since 20 years

Well tolerated by most patients

No recalls since 30 years

Data confirms it's a safe medication

Thyroid

What is the best treatment?

Compare the effect of combination therapy with thyroxine (T_4) and T_3 versus T_4 monotherapy
Double-blind, randomised cross-over.
Tests for quality of life (QOL) and depression
59 patients (55 women); median age 46 years.

49% percent preferred the combination and 15% monotherapy

treatment groups, T_4/T_3 combination therapy T_3 (20 μg) given once daily seemed superior to T_4 monotherapy

Desiccated thyroid contains T3 and T4!

Hypothyroidism

2009 study suggests that it's possible that a subgroup of patients with a polymorphism in the type 2 deiodinase might benefit from combined therapy.

15% of patients do not respond to levothyroxine

Only randomized studies comparing desiccated to levothyroxine

ical Endocrinology & Metabolism

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ORIGINAL ARTICLE

Endocrine Care

Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study

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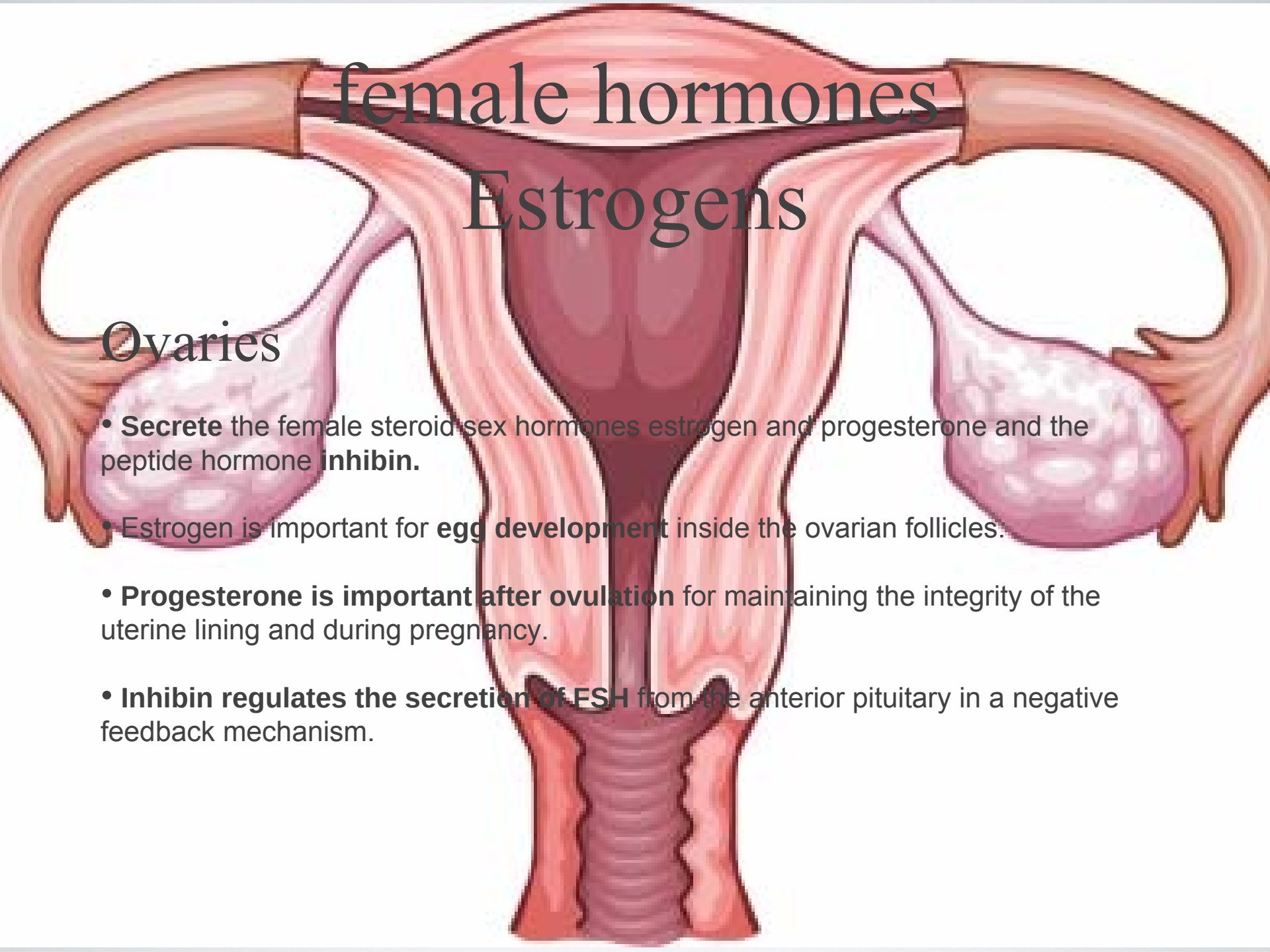
Context: Patients previously treated with desiccated thyroid extract (DTE), when being switched to levothyroxine (L-T_4), occasionally did not feel as well despite adequate dosing based on serum TSH levels.

Objective: Our objective was to investigate the effectiveness of DTE compared with L-T_4 in hypothyroid patients.

Design and Setting: We conducted a randomized, double-blind, crossover study at a tertiary care center.

Patients: Patients (n = 70, age 18–65 years) diagnosed with primary hypothyroidism on a stable dose of L-T_4 for 6 months were included in the study.

female hormones
Estrogens



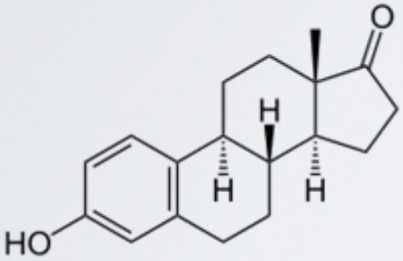
Ovaries

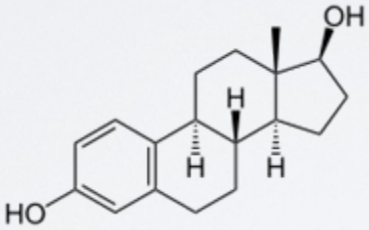
- **Secrete** the female steroid sex hormones estrogen and progesterone and the peptide hormone **inhibin.**
- Estrogen is important for **egg development** inside the ovarian follicles.
- **Progesterone is important after ovulation** for maintaining the integrity of the uterine lining and during pregnancy.
- **Inhibin regulates the secretion of FSH** from the anterior pituitary in a negative feedback mechanism.

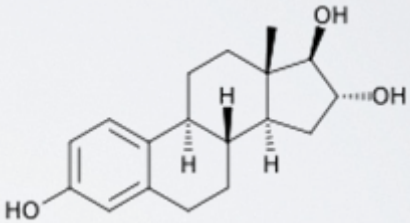
estrogens

3 types of estrogens:

E1: Estrone E2: Estradiol E3: Estriol







Produced during menopause **Predominant in nonpregnant women** **Primary estrogen of pregnancy**

- From menarche to menopause the primary estrogen is 17β-estradiol.
- In postmenopausal women more Estrone is present than Estradiol.
- Estrone is weaker than estradiol

estrogens

•Structural
•promote formation of female secondary sex characteristics
•accelerate metabolism
•reduce muscle mass
•increase fat stores
•stimulate endometrial growth
•increase uterine growth
•increase vaginal lubrication
•thicken the vaginal wall
•maintenance of vessel and skin
•reduce bone resorption, increase bone formation
•morphic change (endomorphic -> mesomorphic -> ectomorphic)
•protein synthesis
•increase hepatic production of binding proteins
•coagulation
•increase circulating level of factors 2, 7, 9, 10, plasminogen
•decrease antithrombin III
•increase platelet adhesiveness

•Lipid
•increase HDL, triglyceride
•decrease LDL, fat deposition
•Fluid balance
•salt (sodium) and water retention
•increase cortisol, SHBG
•Gastrointestinal tract
•reduce bowel motility
•increase cholesterol in bile
•Melanin
•increase pheomelanin, reduce eumelanin
•Cancer
•support hormone-sensitive breast cancers
•Lung function
•promotes lung function by supporting
•alveoli (in rodents but probably in humans).

Menopause

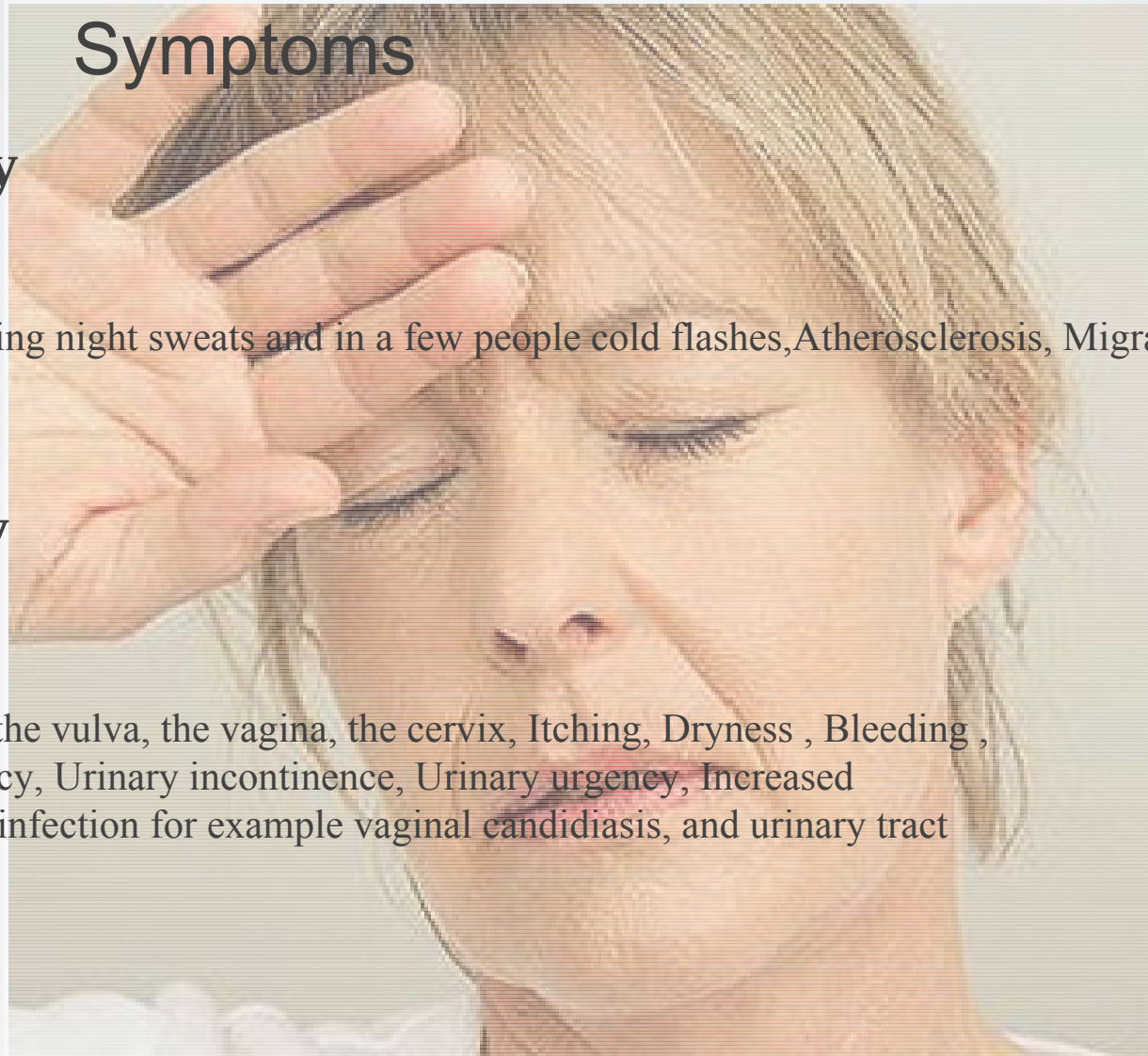
Symptoms

Vascular instability

•Hot flashes or hot flushes, including night sweats and in a few people cold flashes,Atherosclerosis, Migra
Rapid heart beat

Urogenital atrophy

- Thinning of the membranes of the vulva, the vagina, the cervix, Itching, Dryness , Bleeding , Watery discharge, Urinary frequency, Urinary incontinence, Urinary urgency, Increased susceptibility to inflammation and infection for example vaginal candidiasis, and urinary tract infections



MENOPAUSE

Symptoms

Skeletal

Back pain, Joint pain, Muscle pain, Osteopenia and the risk of osteoporosis gradually developing over time

Skin, soft tissue

Breast atrophy, breast tenderness +/- swelling,Decreased elasticity of the skinFormication (itching, tingling, burning, pins and needles, or sensation of ants crawling on or under the skin)Skin thinning and becoming drier

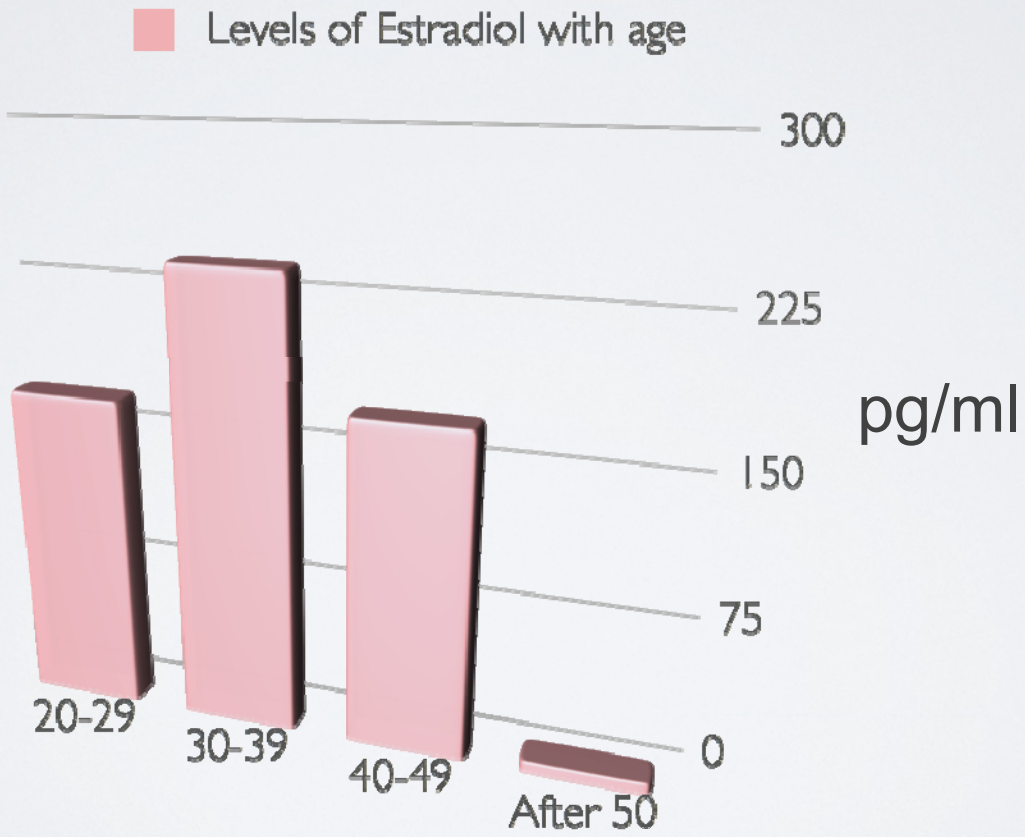
Psychological

Depression and/or anxiety, Fatigue Irritability Memory loss, and problems with concentration Mood disturbance Sleep disturbances, poor quality sleep, light sleep, insomnia

Sexual

Dyspareunia or painful intercourse Decreased libido Problems reaching orgasm Vaginal dryness and vaginal atrophy

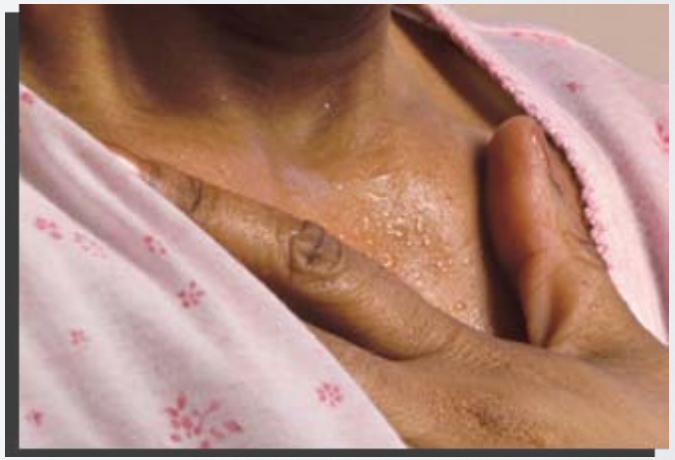
Estradiol replacement therapy



Frequency of symptoms

Table-1: Clinical presentation of menopause.

Vasomotor symptoms 85% of peri- and 66% of postmenopausal women
Uro-Genital symptoms (atrophic vaginitis) 50-70% of postmenopausal women
Psychological disturbance 10%
Osteroporosis 30%
Gynaecological malignancy 10%
Post-menopausal bleeding 3.3%
Back pain 1%



BHRT Treatment

Indication:

Symptoms of menopause

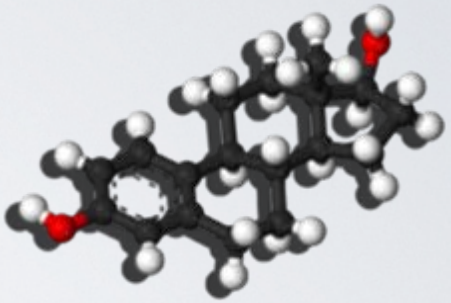
Contraindication:

Allergy to the drug
Endometrial cancer (estrogen dependent) or hyperplasia
Breast Cancer or history of breast cancer
Liver disease and cancer
Abnormal genital bleeding (undiagnosed)
history of arterial thromboembolic disease
DVT
Loss of vision (if due to vascular disease)

Treatment

Availability of Estradiol:

Oral: Estrace (Canada), Zumenon (UK). Be careful of oestradiol valerate (not bioidentical)



Transdermal: Climara (25 to 100 microg/day)
ESTRADERM (UK)
ESTRADOT
ESTROGEL
SANDOZ ESTRADIOL DERM 50, 75 and 100

Vaginal ring : Estring (UK, Canada)

Tablet: Vagifem (UK, Canada)

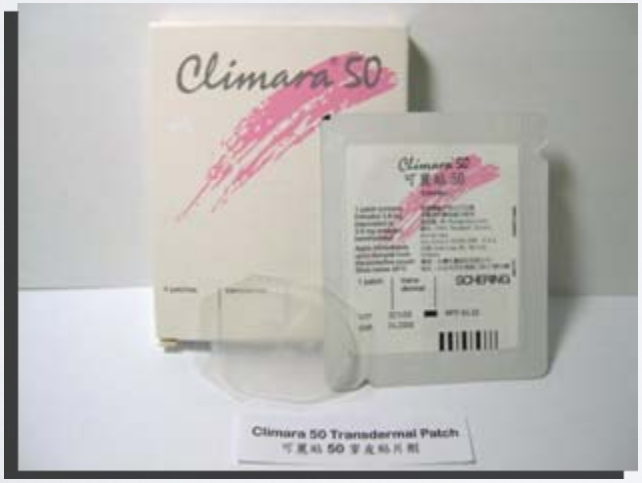
Oral is currently the most commonly utilized route of administration in the United States.

Transdermal drug delivery may mitigate some of these effects by avoiding gut and hepatic first-pass metabolism.

Treatment


zumenon
Estradiol
2 mg comprimido revestido por película

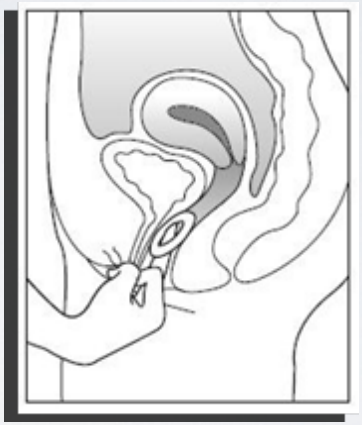

Estrace
Estrace (estradiol)
0.5 mg
1 mg
2 mg
USES: Estrogens are hormones used for replacement in women who are no longer producing proper amounts. This medication is used to treat symptoms associated with menopause.

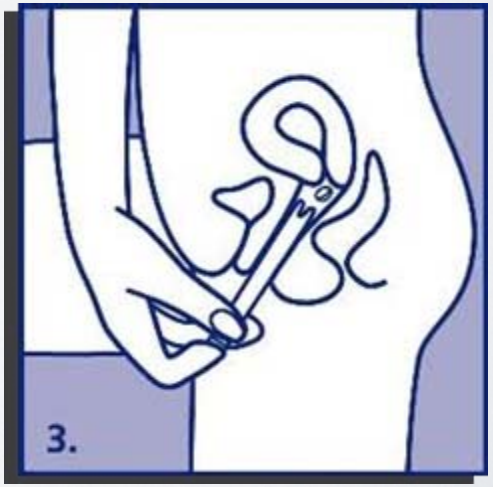

Climara 50
Climara 50 Transdermal Patch


ESTRADERM
0.05
ESTRADERM
0.05

Treatment

The ring should be pressed into an oval and inserted into the upper third of the vaginal vault





TREATMENT

Oral vs transdermal:
Pharmacokinetic differences

- oral estrogens must be administered in relatively high doses
- Pass the gut and hepatic first pass
- variations in the metabolism of oral estrogens
- elevated TGs or hypertension

ORAL	TRANSDERMAL PATCH
Higher risk of DVT	Lower risk of DVT
Increase the TG levels	No increase in TG
	Better for libido
	Fewer systemic adverse effects(vaginal bleeding, breast tenderness)

Orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates

Transdermal administration produces therapeutic plasma levels of estradiol with lower circulating levels of estrone

Efficacy

Vasomotor symptoms

Study in sweden

459 early postmenopausal non-hysterectomized women

primary endpoint was change in frequency and severity of moderate to severe hot flushes at 12 week

estradiol valerate (E2V) and medroxyprogesterone acetate (MPA)

The frequency of hot flushes was reduced by >or=70% after one month

Study in UK

577 postmenopausal women were enrolled

0.5 mg 17beta-estradiol + 0.1 mg NETA

Low-dose transdermal estradiol gel 0.1%

significant decrease in the frequency and severity of hot flushes was achieved by week 3

Similar results with gel estradiol gel 0.1%(0.25mg)

2 mg estriol in 168 postmenopausal patients was markedly effective in 22.6% of cases, effective in 45.2%, fairly effective in 14.3%, and ineffective in 17.9% of cases

Estriol not accepted by Health Canada but estradiol has a similar effectiveness profile

Efficacy

Atrophic vaginitis

Systemic (oral) vs local (cream, tablet,ring)

Local seams to have similar efficacy then systemic

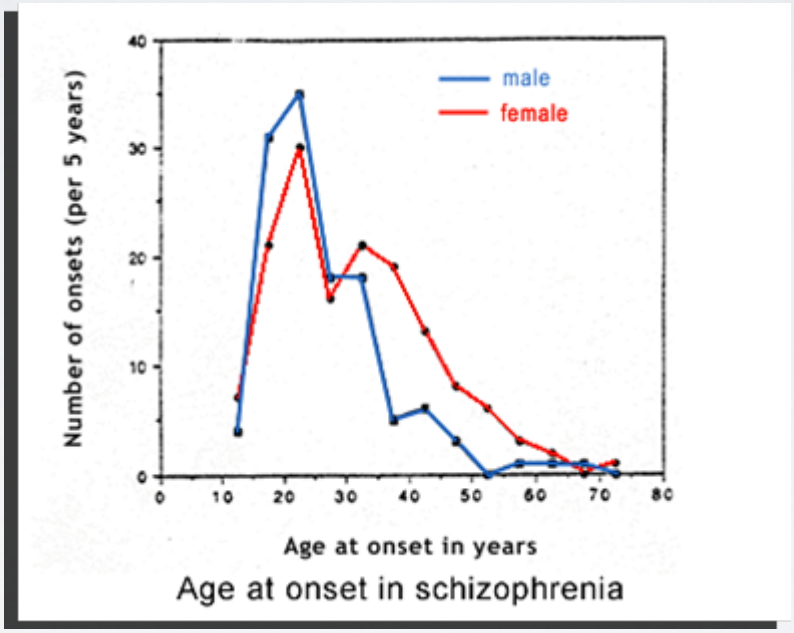
230 patients were randomized to receive either placebo, 17β-estradiol 10 μg or Vagifem® (25 μg estradiol)
Patients inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 10 weeks.
Less dryness, soreness and irritation then placebo

Cream,tablets,ring have similar efficacy in randomized studies

Efficacy

Psychological disturbance

Schizophrenia



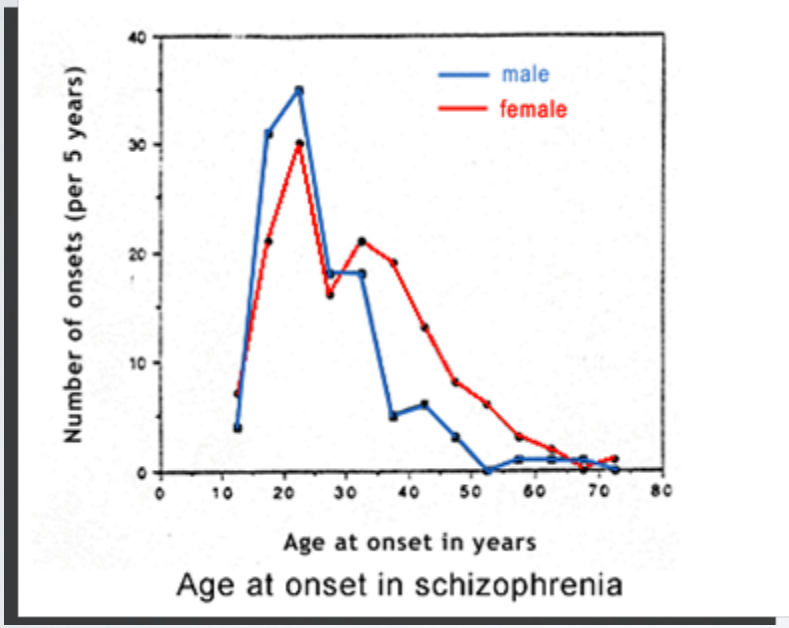
Age at onset in schizophrenia

BHRT Works on younger menopausal women

Efficacy

Psychological disturbance

Schizophrenia



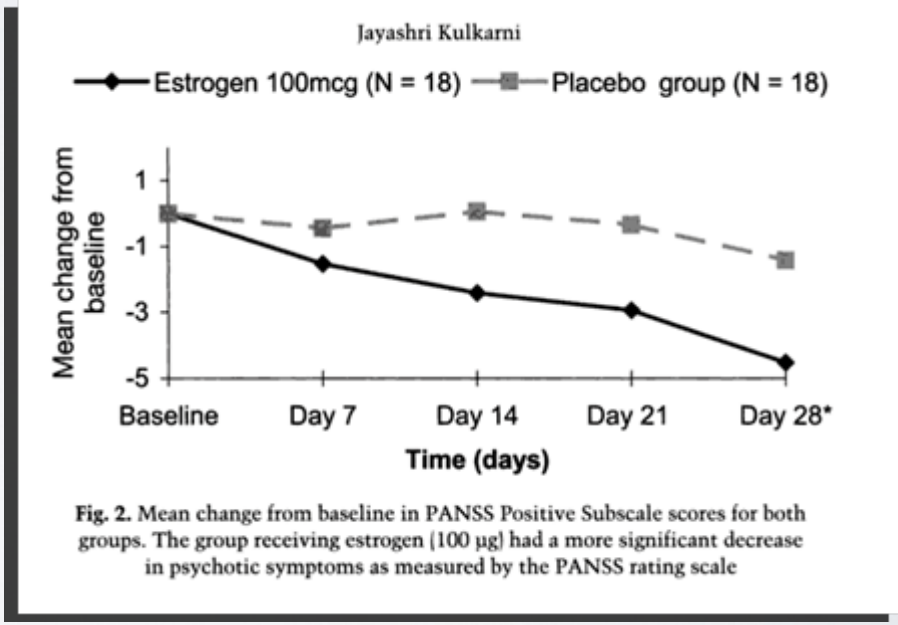


Fig. 2. Mean change from baseline in PANSS Positive Subscale scores for both groups. The group receiving estrogen (100 µg) had a more significant decrease in psychotic symptoms as measured by the PANSS rating scale

BHRT Works on younger menopausal women

Efficacy

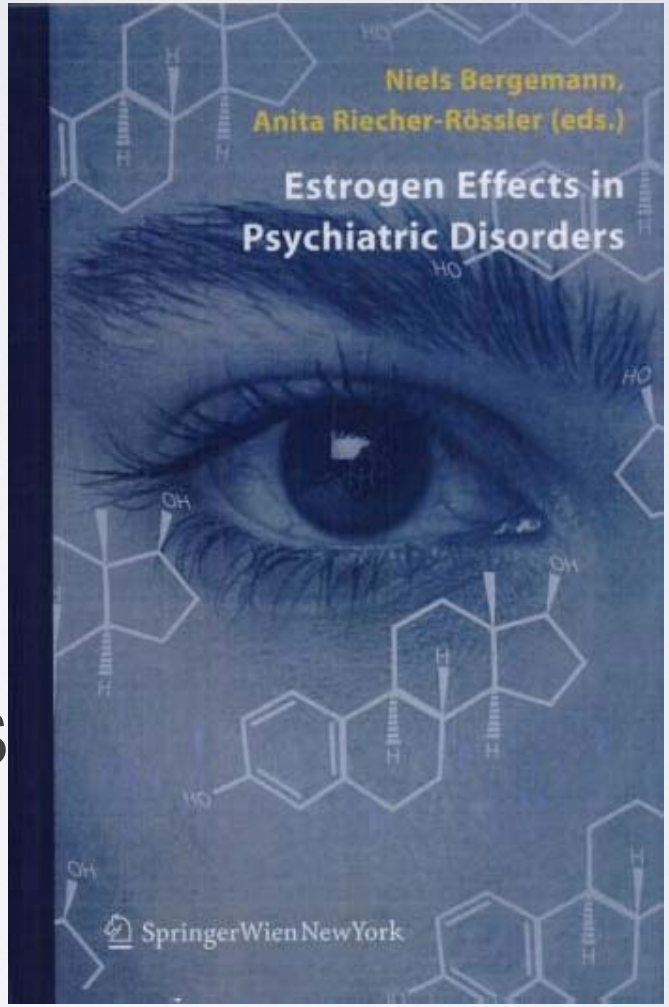
Psychological disturbance

SCHIZOPHRENIA

DEPRESSION

PERIMENOPAUSAL AFFECTIVE DISORDERS

ALZHEIMERS



Efficacy

Psychological disturbance

ovarian hormones modulate serotonin and noradrenaline neurotransmission

2 double-blind, placebo-controlled trials with similar results

34 perimenopausal women with depression

After 3 weeks of estradiol, depression rating scale scores were significantly decreased

1 randomized study did not get those results

Younger perimenopausal, but not older postmenopausal, depressed women respond to short-term estradiol therapy

87 patients all randomized => NO DIFFERENCE WITH PLACEBO. They took women 5-10 years post natural menopause

BHRT Works on younger menopausal women

effects of low-dose 17beta-estradiol and norethisterone (hormone therapy [HT]) versus placebo in women with Alzheimer Disease (AD)

HT may reduce depressive mood and give less cognitive decline.

Efficacy

Osteoporosis

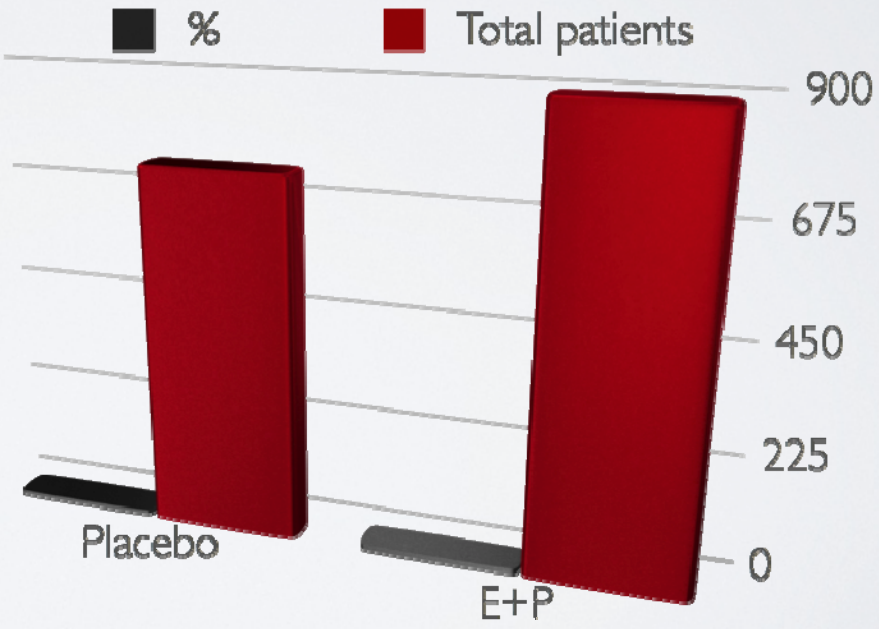
The North American Menopause Society position is to treat young menopausal women

BHRT works for osteoporosis

Women's Health Initiative showed that postmenopausal hormone replacement therapy (HRT) prevents fractures

25% to 29% lower risk of osteoporotic fracture (P < 0.0001) in 1 year

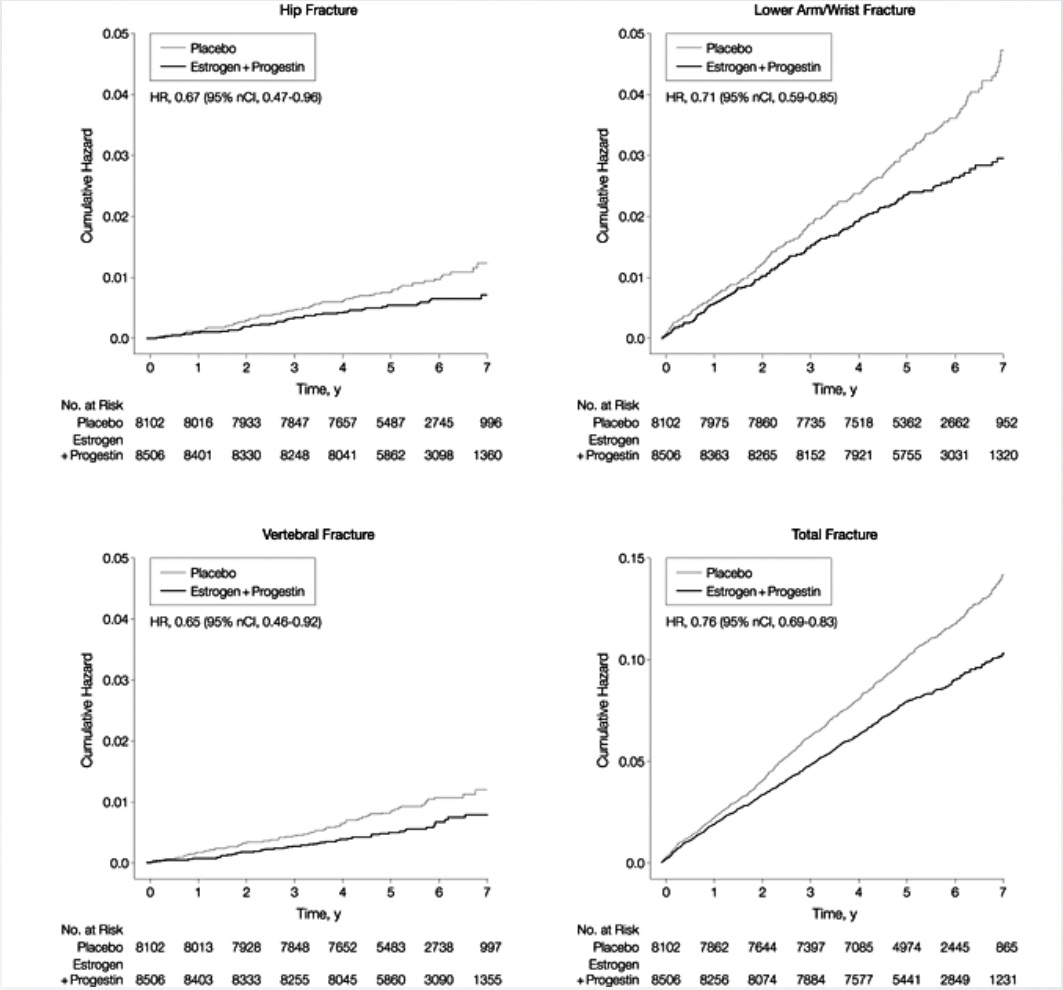
Women who had stopped HRT more than 5 years had similar fracture then non users



Efficacy

Osteoporosis

HIP
ARM
VERTEBRAL
FRACTURE
WERE
LOWER
WITH HRT



EFFICACY

Estrogen is an effective treatment for Menopause

- Start treatment early for better results
- Good for vasomotor symptoms.
- Good for treating atrophic vaginitis
- Good to prevent osteoporosis.

- Hormone replacement therapy reduced total mortality in trials with mean age of participants under 60 years.
- No change in mortality was seen in trials with mean age over 60 years.

SAFETY

Breast cancer

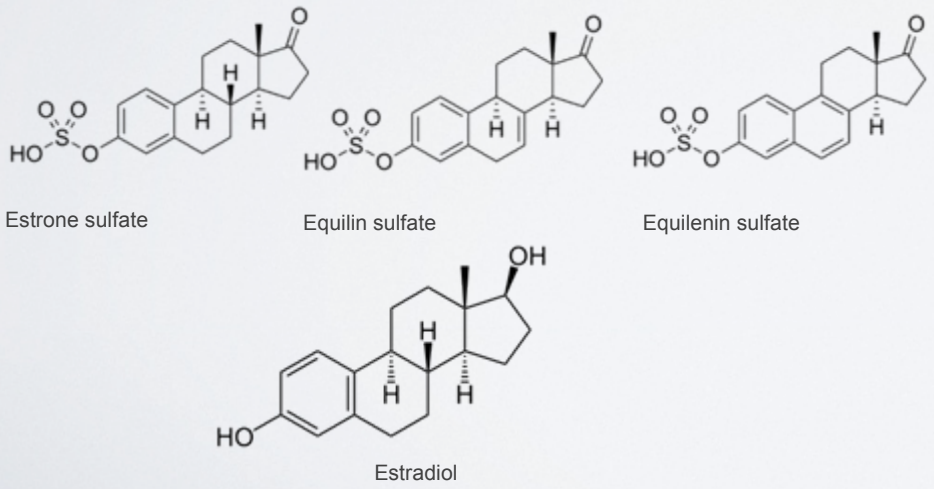
WHI study (2002) :

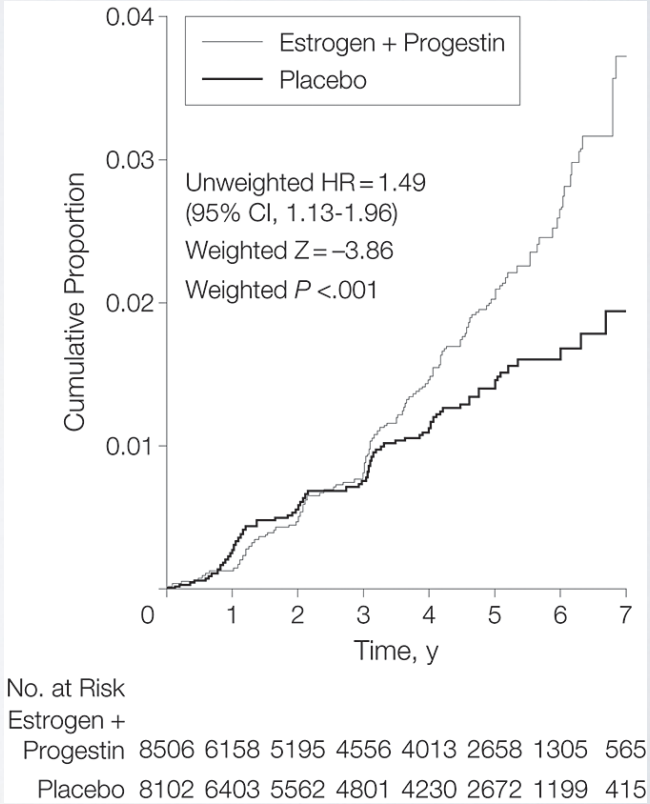
Continuous combined HRT was associated with an increased breast cancer risk if used for four years or more
However this increased risk dissipates quickly once use is discontinued.

Increased risk of breast cancer that was 1.29 times those who never used estrogen
Synthetic progestin was used in combination with estrogen 1.69 times

<u>They did not use Bioidentical hormones in WHI</u>

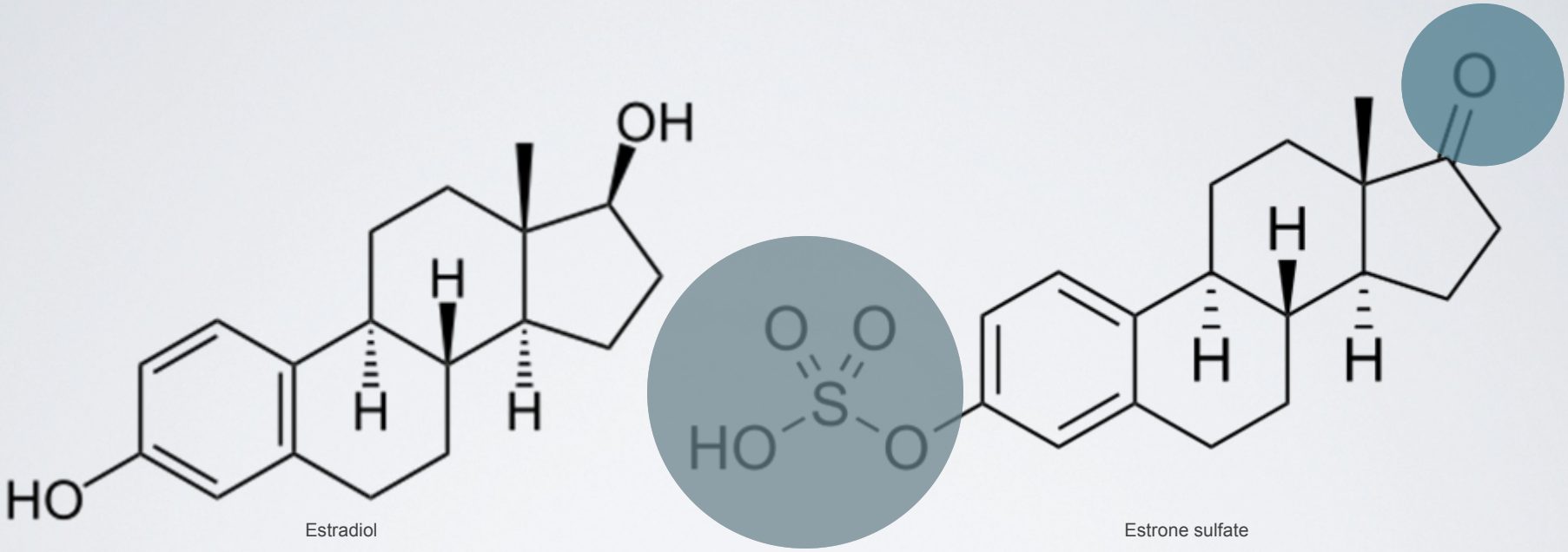
conjugated equine estrogens vs Bioidentical estradiol (premarin)





SAFETY

Bioidentical estradiol (premarin) vs Conjugated equine estrogens



Estradiol

Estrone sulfate

Mr Good Guy

Mr Bad Guy

Safety

Breast cancer

Institut National de la Santé et de la Recherche Médicale
Compared the association between different HRTs and breast cancer risk

Results from the E3N cohort study

2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women
Relative risk was

1.00 (0.83–1.22) for estrogen–progesterone
1.16 (0.94–1.43) for estrogen–dydrogesterone
1.69 (1.50–1.91) for estrogen combined with other progestagens.

No risk of breast cancer when Bioidentical progesterone was used.

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Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study

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Abstract

Large numbers of hormone replacement therapies (HRTs) are available for the treatment of menopausal symptoms. It is still unclear whether some are more deleterious than others regarding breast cancer risk. The goal of this study was to assess and compare the association between different HRTs and breast cancer risk, using data from the French E3N cohort study. Invasive breast cancer cases were identified through biennial self-administered questionnaires completed from 1990 to 2002. During follow-up (mean duration 8.1 postmenopausal years), 2,354 cases of invasive breast cancer occurred among 80,377 postmenopausal women. Compared with HRT never-use, use of estrogen alone was associated with a significant 1.29-fold increased risk (95% confidence interval 1.02–1.65). The association of estrogen-progestagen combinations with breast cancer risk varied significantly according to the type of progestagen: the relative risk was 1.00 (0.83–1.22) for estrogen–progesterone, 1.16 (0.94–1.43) for estrogen–dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestagens. This latter category involves progestins with different physiologic activities (androgenic, nonandrogenic, antiandrogenic), but their associations with breast cancer risk did not differ significantly from one another. This study found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal/percutaneous). These findings suggest that the choice of the progestagen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone or dydrogesterone.

Safety

Breast cancer

Finnish study

Cohort included 110 984 postmenopausal women aged over 50 (from national cancer registry) who had used estrogen alone for more than six months

Women who took estradiol orally or transdermally (with no progesterone) for **less than five years were no more likely to get breast cancer** than women of a similar age in the general Finnish population

Longer use of systemic therapy was associated with a significant rise in breast cancer incidence (ratio 1.44 (1.29 to 1.59)).

Link between breast cancer and long term treatment with oral or transdermal estradiol in postmenopausal Finnish women

Use of estrogen alone for less then 5 years to lower risk of breast cancer

Safety

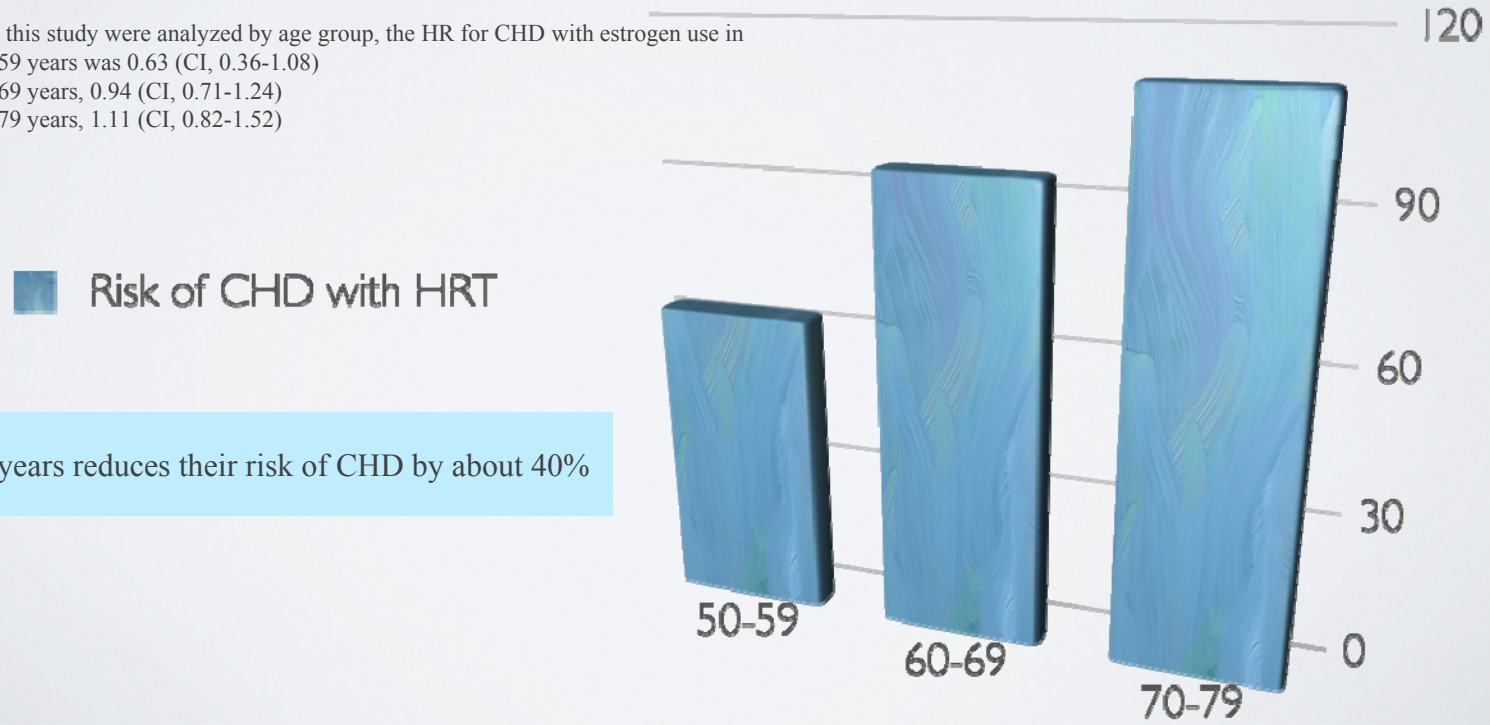
Coronary artery disease, Stroke, DVT

1990's it was though that estrogen alone can lower the risk of cardiovascular diseases.

Incidence of myocardial infarction (MI) is much more common in men than in women before age 50

WHI enrolled 161,809 postmenopausal women between 1993 and 1998 for this series of trials.
Increased risk of CHD (acute MI), silent MI, or CHD death, with a hazard ratio (HR) of 1.29 (CI, 1.02-1.63).

When the data from this study were analyzed by age group, the HR for CHD with estrogen use in
women aged 50 to 59 years was 0.63 (CI, 0.36-1.08)
women aged 60 to 69 years, 0.94 (CI, 0.71-1.24)
women aged 70 to 79 years, 1.11 (CI, 0.82-1.52)

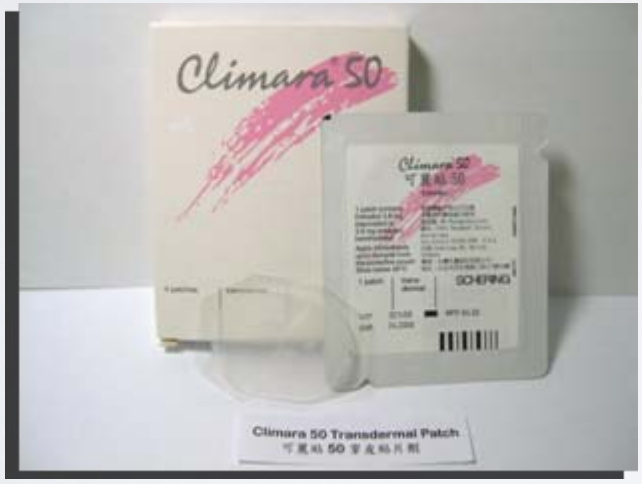


Age 50 to 59 years reduces their risk of CHD by about 40%

SAFETY

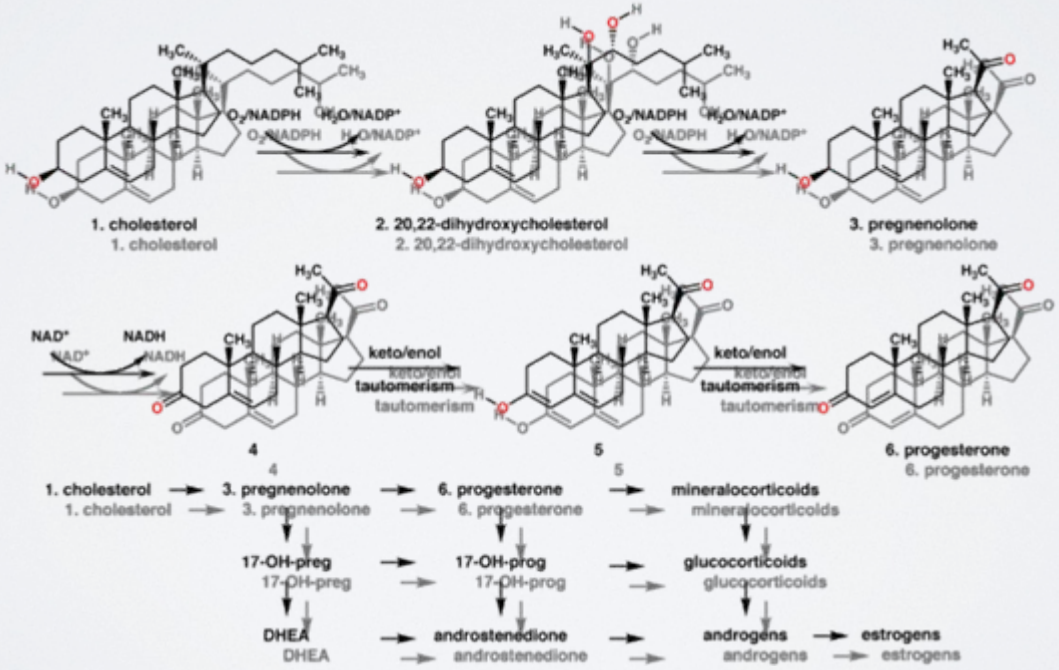
Transdermal estradiol

In contrast to oral estrogen, which causes a 3- to 4-fold increased risk of venous thromboembolism (VTE), transdermal estrogen does not appear to increase the risk of VTE.



PROGESTERONE

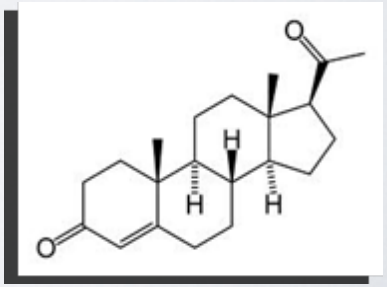
- Progesterone is produced in the ovaries (corpus luteum), the adrenals and placenta
- Stored in adipose (fat) tissue
- Placenta produces about 250 mg progesterone per day
- Progesterone in milk
- Synthesized from Cholesterol



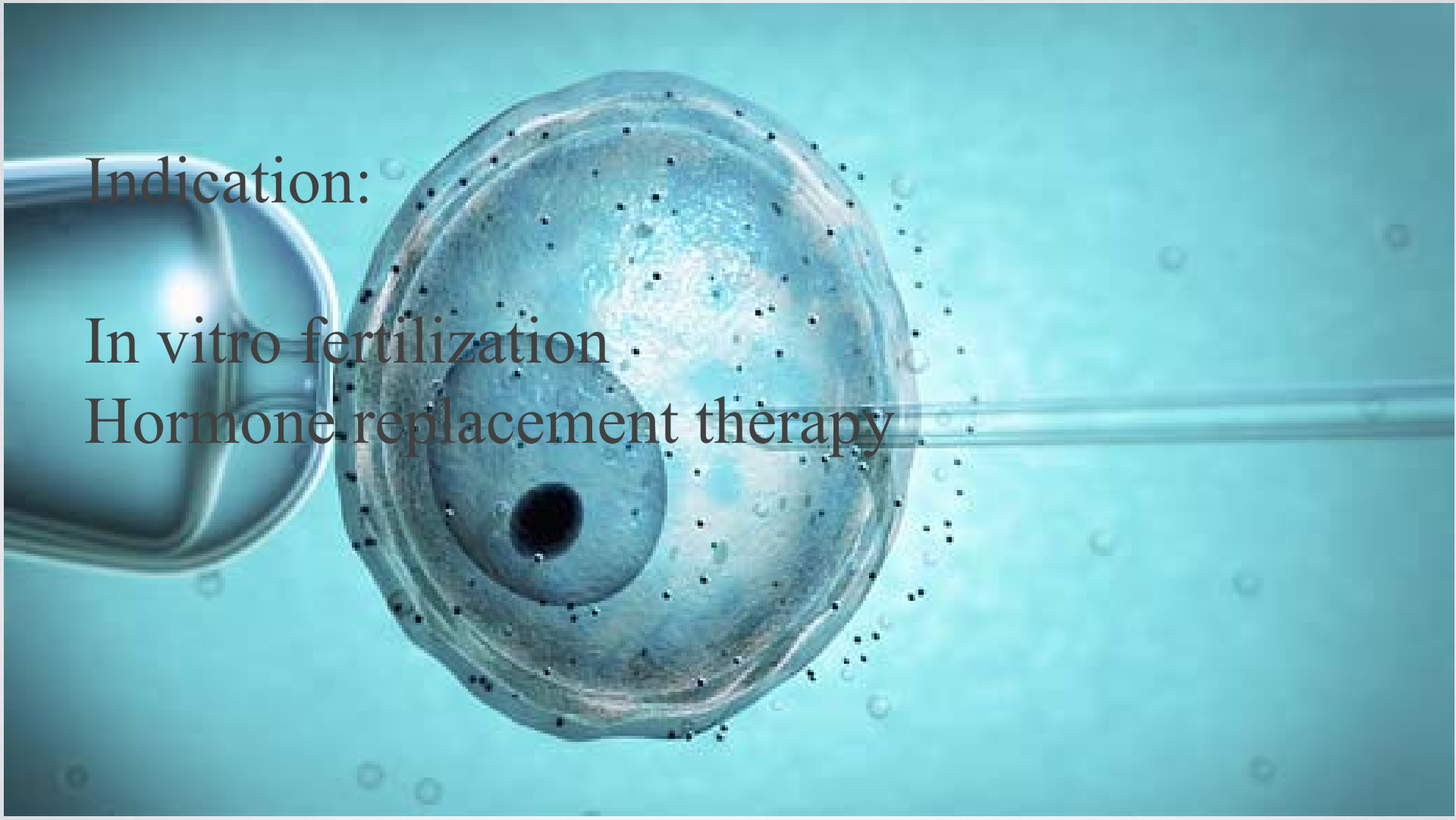
Progesterone

Reproductive system

- "Hormone of **pregnancy**"
- Many roles relating to the **development of the fetus**
- Converts the endometrium to secretory stage to **prepare the uterus for implantation**
- Affects the **vaginal epithelium** and cervical mucus
- If pregnancy does not occur, progesterone levels will decrease, leading to menstruation
- Normal menstrual bleeding is progesterone withdrawal bleeding.
- Progesterone **decreases contractility of the uterine smooth muscle**.
- **Inhibits lactation** during pregnancy.
- The fall in progesterone levels following delivery is one of the triggers for **milk production.**
- **Increases core temperature during ovulation**.
- Reduces spasm and relaxes smooth muscle.
- Acts as an **antiinflammatory agent** and regulates the immune response.
- **Reduces gall-bladder activity**



progesterone



Indication:

In vitro fertilization

Hormone replacement therapy

progesterone

Contraindicated:

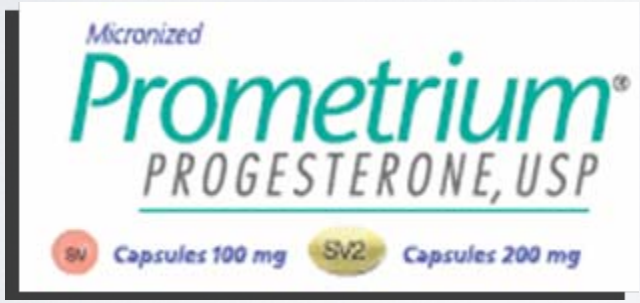
- Undiagnosed vaginal bleeding,
- Liver dysfunction or disease,
- Known or suspected malignancy of the breast or genital organs,
- Known or suspected progesterone-dependent neoplasia,
- Known sensitivity to progesterone
- Missed abortion,
- Thrombophlebitis, thromboembolic disorders, cerebral apoplexy or patients with a history of these conditions,
- Acute porphyria

progesterone

Route of administration

Oral: PROMETRIUM (micronized progesterone)
Gel: Crinone (8% gel)
Intra-muscular: PROGESTERONE INJ 50MG/ML

Micronized: decreased destruction in the gastrointestinal tract, a longer half-life, and enhanced bioavailability

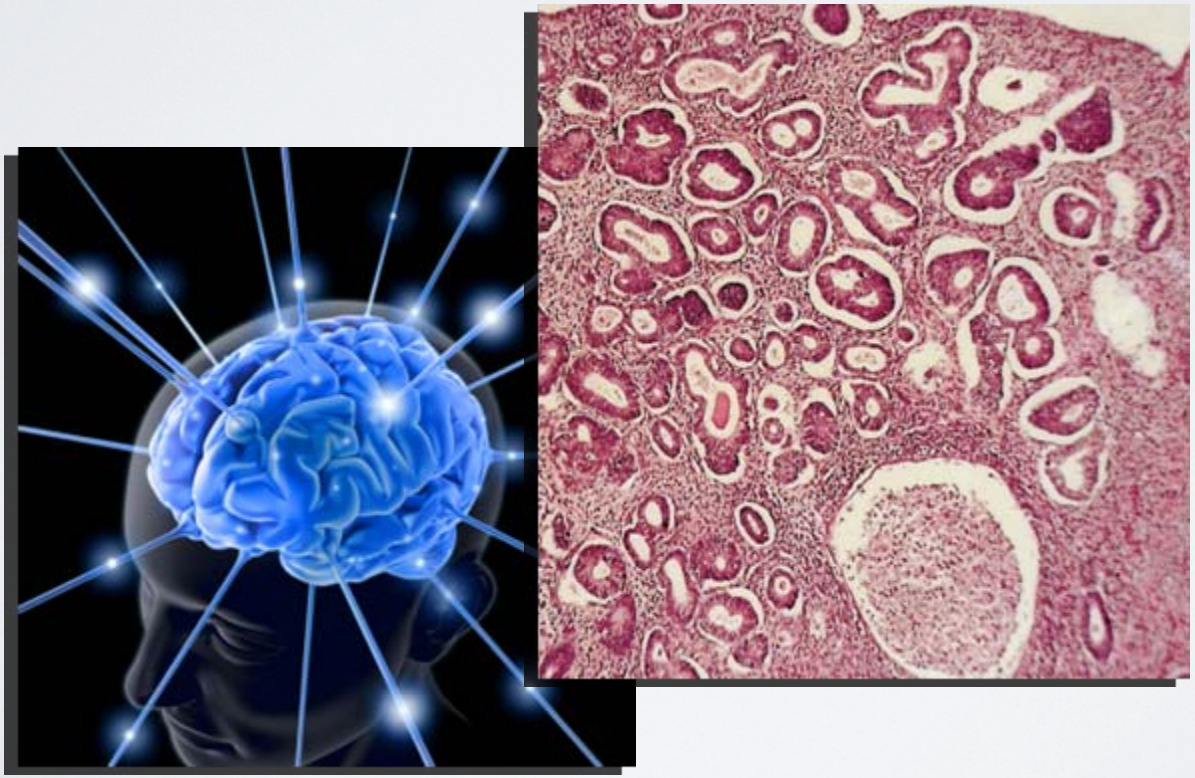


200 mg daily for the last 14 days of estrogen treatment per cycle
(i.e. from day 8 to day 21 for a 28-day cycle, and from day 12 to day 25 for a 30-day cycle)

1.125 g CRINONE 8% Vaginal Gel
From the day of embryo transfer

Efficacy of progesterone

In HRT for menopause: used to oppose the effects of estrogen
Endometrial protection: preventing uterine hyperplasia and malignancy in response to estrogens
Neuroprotective and neurotrophic effects



Efficacy of progesterone

Blood vessels

Low dose : No vascular toxicity
MPA : Vascular toxicity

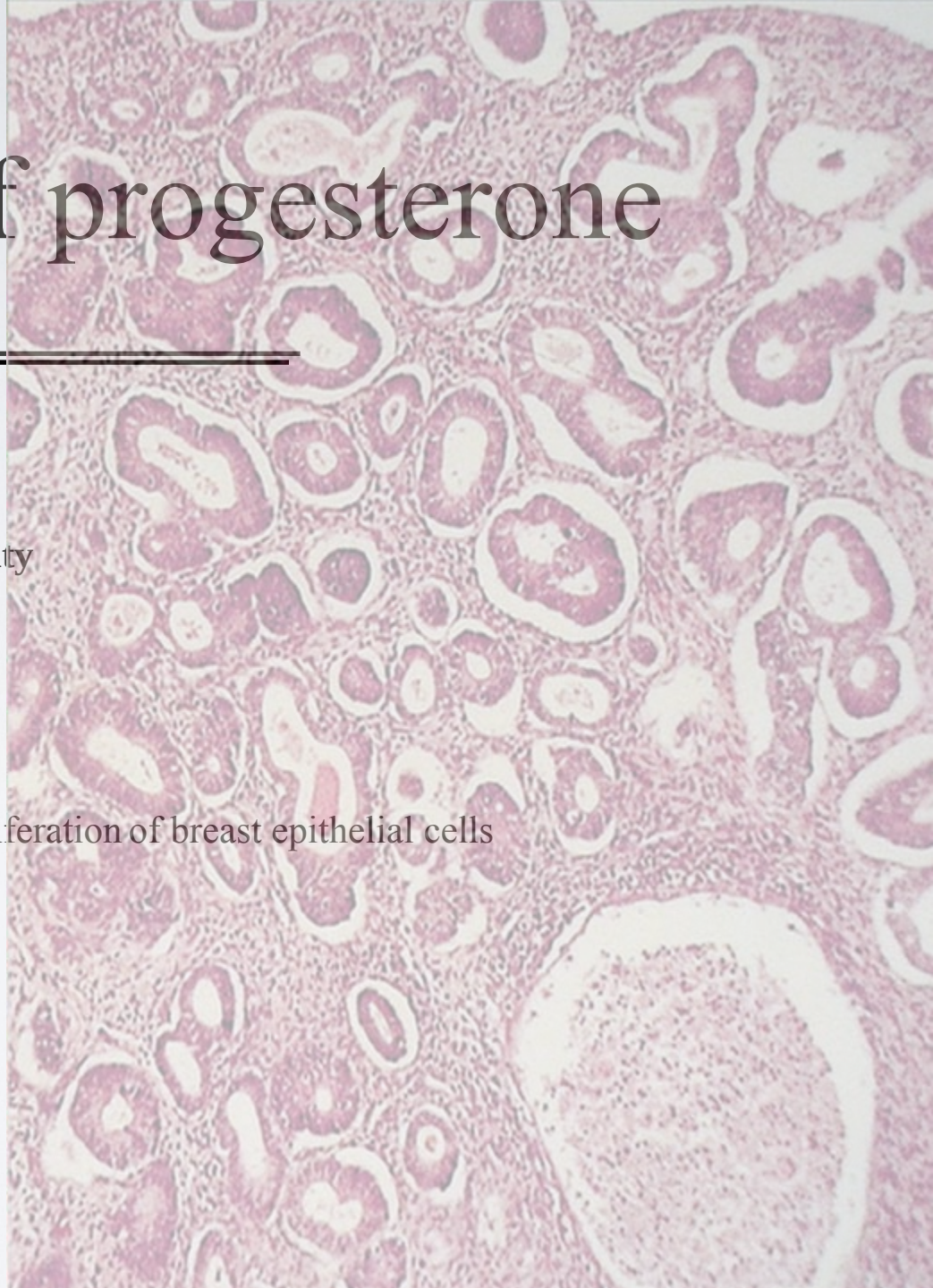
Mammary glands

Low dose: No mitotic effect
High dose: Stimulate the proliferation of breast epithelial cells

Bones

promote bone formation

Reduce the risk of endometrial hyperplasia



Efficacy of progesterone

PEPI Trial : no significant bone-protective effect (both with bioidentical and MPA)

Postmenopausal Estrogen/Progestin Interventions (PEPI) trial

875 healthy postmenopausal women aged 45 to 64 years at seven clinical centers in the U.S.

(1). Placebo

(2). 0.625 mg of estrogen per day

(3) 0.625 mg of estrogen per day plus 10 mg of a synthetic progestin taken daily for 12 days,

(4) 0.625 mg of estrogen daily plus 2.5 mg of synthetic progestin taken daily

(5) 0.625 mg of estrogen daily plus 200 mg of a natural (micronized) progesterone (MP) taken daily for 12 days per month.

Efficacy of progesterone

Results

70 and 90 percent of the increase in BMD occurred during the first year of the study

No difference between the groups with or without progesterone (bioidentical or not)

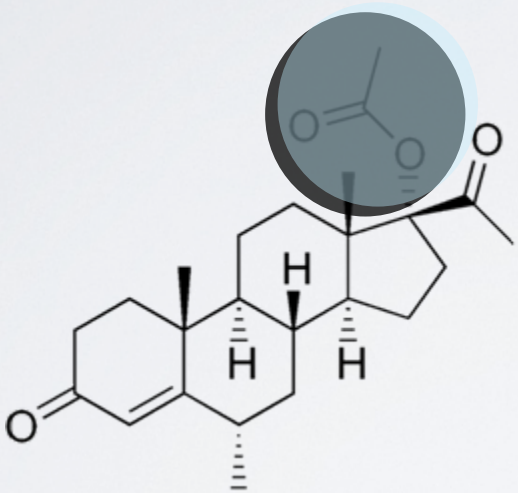
Does adding progesterone really helps decrease fracture ?

Datas shows that estrogen is more important

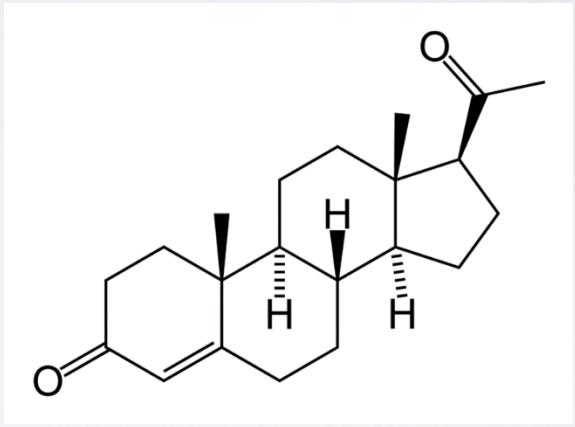
Safety progesterone

The Heart and Estrogen/Progestin Replacement Study (HERS) Trial

compared the effects of conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA) treatment with placebo
increase in coronary heart disease during the first year of hormone treatment and no overall cardiovascular benefit with longer follow-up



medroxyprogesterone acetate (MPA)



progesterone

MPA = Experimental carcinogen, neoplastigen, tumorigen, teratogen.

Progesterone = Limited evidence that this may be a possible carcinogen

Safety Progesterone

French cohort (E3N cohort)
54,548 postmenopausal women

No risk of having Breast cancer 8 years after treatment when Bioidentical progesterone was used instead of MPA

Progesterone has a safe pharmaceutical profile

SAFETY PROGESTERONE

TABLE 6. Adverse Experiences (≥ 2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women Over a 3-Year Period [Percentage (%) of Patients Reporting]

	PROMETRIUM Capsules 200 mg with Conjugated Estrogens 0.625 mg	Placebo
	(n=178)	(n=174)
Headache	31	27
Breast Tenderness	27	6
Joint Pain	20	29
Depression	19	12
Dizziness	15	9
Abdominal Bloating	12	5
Hot Flashes	11	35
Urinary Problems	11	9
Abdominal Pain	10	10
Vaginal Discharge	10	3
Nausea / Vomiting	8	7
Worry	8	4
Chest Pain	7	5
Diarrhea	7	4
Night Sweats	7	17
Breast Pain	6	2
Swelling of Hands and Feet	6	9
Vaginal Dryness	6	10
Constipation	3	2
Breast Carcinoma	2	<1
Breast Excisional Biopsy	2	<1
Cholecystectomy	2	<1

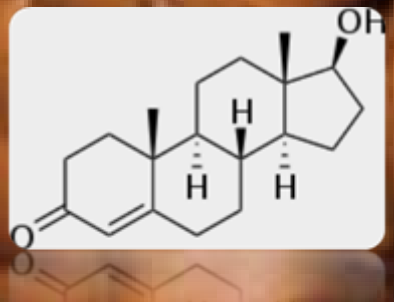
Progesterone is safe - Pregnant women can prove it!

Testosterone

Testosterone is a hormone produced primarily in the testes. helps maintain:

- Bone density
- Fat distribution
- Muscle strength and mass
- Red blood cell production
- Sex drive
- Sperm production

Testosterone level gradually declines with age after age 30.



testosterone

Symptoms of testosterone deficiency

Changes in sexual function.

reduced sexual desire

fewer spontaneous erections

infertility.

Changes in sleep patterns.

insomnia

other sleep disturbances.

Emotional changes.

decrease in motivation or self-confidence

feel sad or depressed

trouble concentrating

Physical changes.

increased body fat

reduced muscle bulk and strength

decreased bone density.

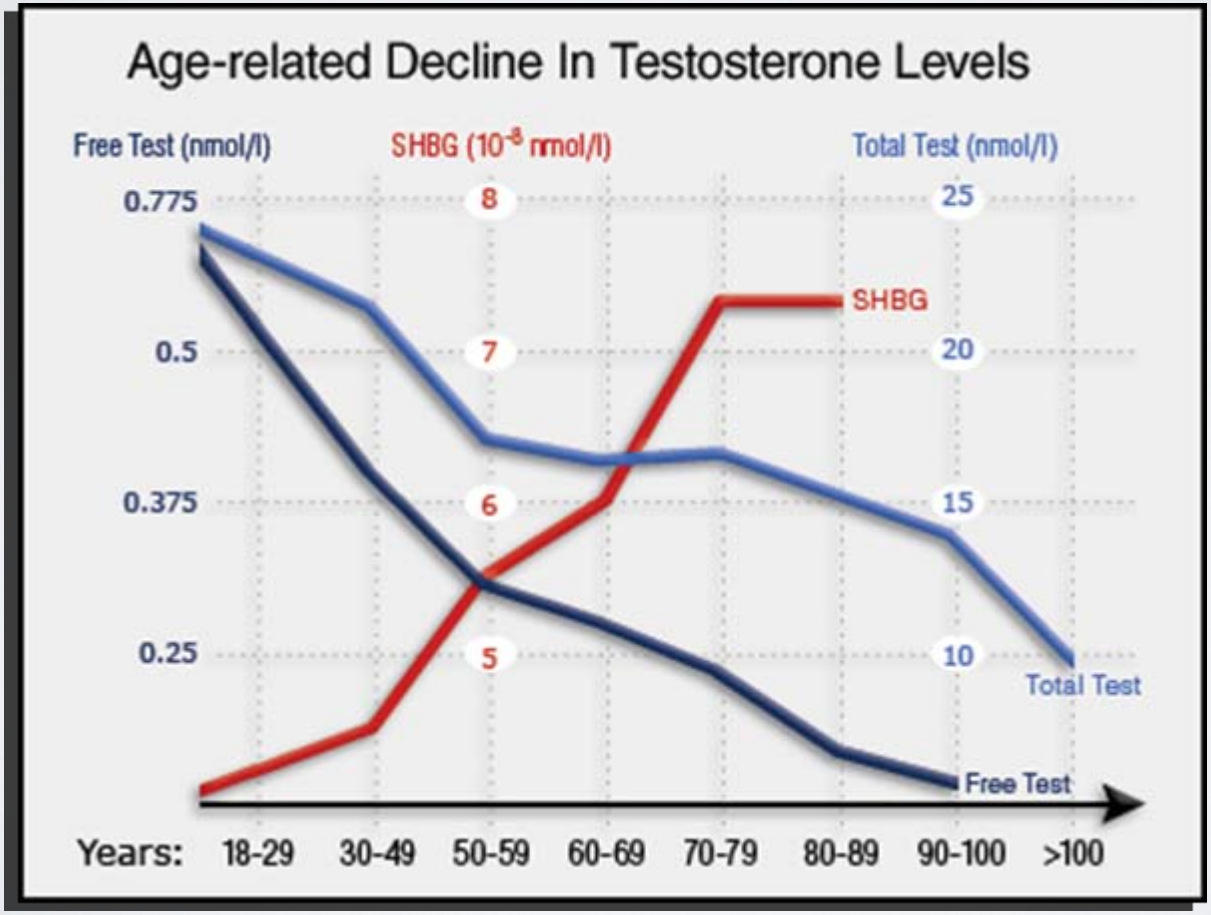
Gynecomastia

hair loss are possible

hot flashes

less energy

Testosterone replacement therapy



testosterone

Indication:

- Testosterone replacement therapy

Contraindication:

- Hypersensitivity
- carcinoma of the prostate or breast
- Women
- Diabetic taking insulin
- Patient on corticosteroid
- Anticoagulant
- Patient on cyclosporine

Available forms

Injectible: testosterone cypionate or testosterone enanthate in oil = NOT BIOIDENTICAL

ORAL: ANDRIOL (TESTOSTERONE UNDECANOATE) = NOT BIOIDENTICAL

Transdermal Patch: ANDRODERM
applied nightly (10:00 PM.) and worn for 24 hours, providing a total dose of 5 mg of testosterone/day.

Gel: ANDROGEL
TESTIM 1%

Efficacy testosterone

TIMES2 Study

220 hypogonadal men with type 2 diabetes
Randomized, double-blind, placebo-controlled study.
Followed them for 1 year
glycemic control was significantly better in the TRT group
Improvements in total and LDL cholesterol, sexual health

Other studies

Beneficial effect of testosterone replacement therapy on Bone Mass Density with improvements over several years.

No convincing evidence of an adverse effect of testosterone replacement therapy on coronary heart disease

Testosterone has a well known efficacy - Just look at body builders

Safety

Adverse events associated with testosterone administration.

209 men (mean age, 74 years)
high prevalence of hypertension, diabetes, hyperlipidemia, and obesity among the participants
testosterone group had higher rates of cardiac, respiratory, and dermatologic events than did the placebo group
testosterone gel was associated with an increased risk of cardiovascular adverse events (23 vs 5)
improvements in leg-press and chest-press strength and in stair climbing while carrying a load

Clinical review : Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis.
51 included studies

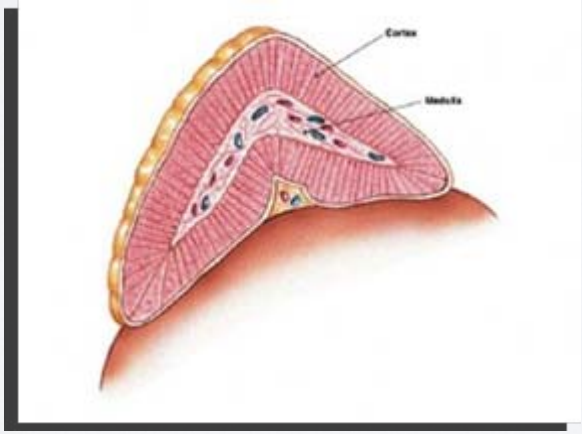
There was no significant effect on mortality, prostate, or cardiovascular outcomes

Health Canada reported 1 case of Prostate Cancer since 2001

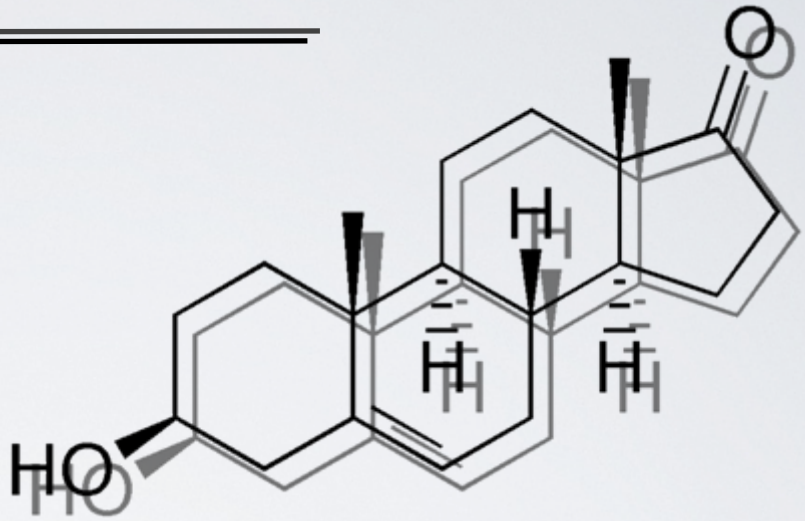
DHEA

Major secretory steroidal product of the adrenal glands
Produced by gonads and brain
most abundant circulating steroid in humans

Measurement:
Diagnosis of adrenal cancer/hyperplasia and polycystic ovary syndrome



DHEA



Used for:

Depression
- Anti-depressant effect
- Diminish cortisol level

Alzheimer disease
- Not effective

Improve memory
- pre-hippocampal memory processing
- prefrontal dependent cognitive abilities during stress

Physical performance

muscle-building

no effect on lean body mass, strength, or testosterone levels

Cardiovascular disease and risk of death

2006 study found no correlation between DHEA levels and risk of cardiovascular disease or death in men

DHEA

Cancer
- anti-proliferative effect
- *increased* risk of developing breast cancer (???????)

Diabetes and carotid atherosclerosis
- inverse relationship between serum DHEA and carotid atherosclerosis

Erectile dysfunction
- Some studies demonstrate that it could be useful

Men over 65
- increase in testosterone
- decrease LDL

Longevity
- 940 men and women ranging from age 21 to 88

following them from 1978 until 2005
- higher DHEA-s levels are a "strong predictor" of longevity in men NOT in women

Improving the function of the immune system
- Can help patient with Lupus

SOLD as supplement in the USA
Canada: Not available although listed as a New Drug

DHEA Safety

- cardiovascular effects such as heart palpitations
- may worsen or increase the risk of cancer (breast)
- estrogen-like properties (can worsen endometriosis, uterine fibroids)
- testosterone-like properties (worsen PCOS)
- It can decrease HDL
- Liver problem
- Report of mania in a few patients with depression or bipolar disorder

Drug interaction - DHEA

- Hormone therapy for breast cancer, such as:
  - Anastrozole (Arimidex®)
  - Exemestane (Aromasin®)
  - Fulvestrant (Faslodex®)
  - Letrozole (Femara®)
  - Tamoxifen (Nolvadex®)

- Various other medications, including (but not limited to):
  - Alprazolam (Xanax®)
  - Amitriptyline (Elavil®)
  - Amiodarone (Pacerone®, Cordarone®)
  - Buspirone (BuSpar®)
  - Citalopram (Celexa®)
  - Felodipine (Plendil®)
  - Fexofenadine (Allegra®)
  - Itraconazole (Sporanox®)
  - Ketoconazole (Nizoral®)
  - Lansoprazole (Prevacid®)
  - Losartan (Cozaar®)
  - Lovastatin (Mevacor®)
  - Midazolam (Versed®)
  - Ondansetron (Zofran®, Zuplenz™)
  - Prednisone (Deltasone®)
  - Sertraline (Zoloft®)
  - Sibutramine (Meridia®)
  - Sildenafil (Viagra®, Revatio®)
  - Simvastatin (Zocor®)
  - Triazolam (Halcion®)
  - Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®).

Thank YOU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