Menopause and Hormonal therapy.

Prescribe with confidence

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Based at Kew – public only

0.8 FTE

ITCHY. BITCHY. SWEATY. SLEEPY. BLOATED. FORGETFUL. ALL DRIED UP

A girl has the most eggs at 24/40 gestation **7000000**

By time of birth only have **2000000**

By the time of puberty **400 000**

Ovulation occurs 400-500X/life in women of the ***developed world***

The term menopause was not coined until 19th century

It is largely a first world problem

Menopause defined

- Not actually a complete depletion of ova
- Due to aging of ovary but also of HPO axis
- Those ova remaining are of poor quality and poorly responsive to FSH, LH.
- Ovulation becomes infrequent resulting in erratic periods and unreliable Estrogen, Progesterone and Testosterone levels.
- Remaining ova become atretic within years of the menopause

- A woman is said to be post-menopausal 12 months after her last menstrual period.

ENDOCRINOLOGY OF MENOPAUSE

FSH levels start rising ~10 years prior to menopause

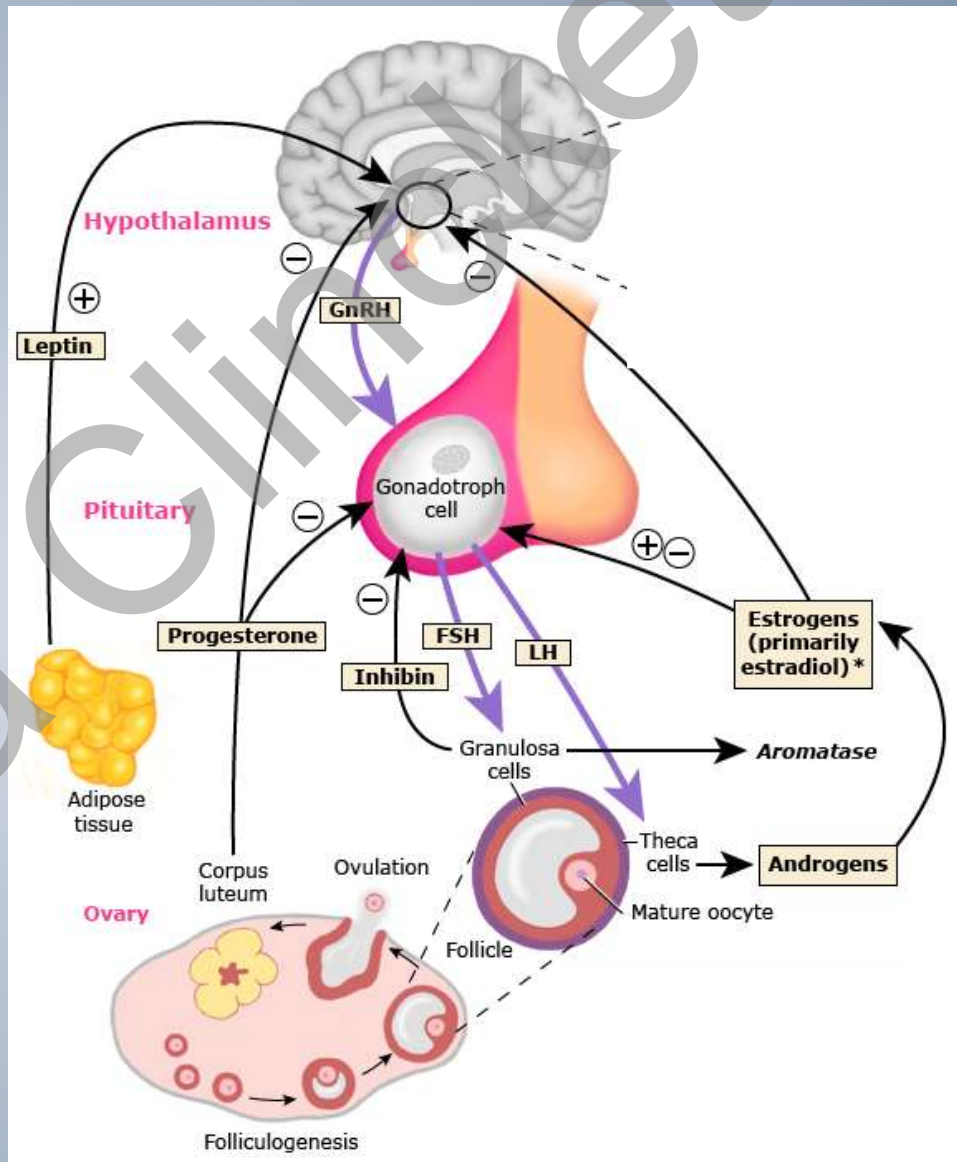
A reduction in granulosa cells in the ovary means less Inhibin production → increased FSH release at the start of each cycle→ increased Estradiol until follicles stop maturing all together

2-3 years AFTER menopause:

- FSH is 10-20X higher

- LH 3 X higher than premen levels

Persistent elevation of both FSH and LH over several months is considered proof of menopause but fluctuation at the perimenopause is common



Endocrinology of Menopause (Testosterone)

- Initially the E:T ratio flips
- Testosterone levels **gradually** decline and ovary stops producing all together ~10 years after menopause
- Androstenedione levels gradually decline by ~50%
- Estrone becomes the predominant Estrogen

Symptoms of Menopause

- Vasomotor
- Urogenital
- Physical
- Skin & hair
- Bones
- Cardiovascular system
- Emotional & cognitive

SYMPTOMS OF MENOPAUSE: VASOMOTOR

"Bouffees de Chaleur"

Hot flushes/flashes

- Affects 80% of women, severe in 30%
- Red face, sweating, heat , rising HR, +/- chills
- Lasts 5-30 mins
- Worse in women with high BMI and smokers
- Lasts on average ~5years
- ~10% will experience them indefinitely
- Night sweats→ sleep disturbance → fatigue
- ~10% experience formication

SYMPTOMS OF MENOPAUSE: UROGENITAL

Dry vagina

Dyspareunia

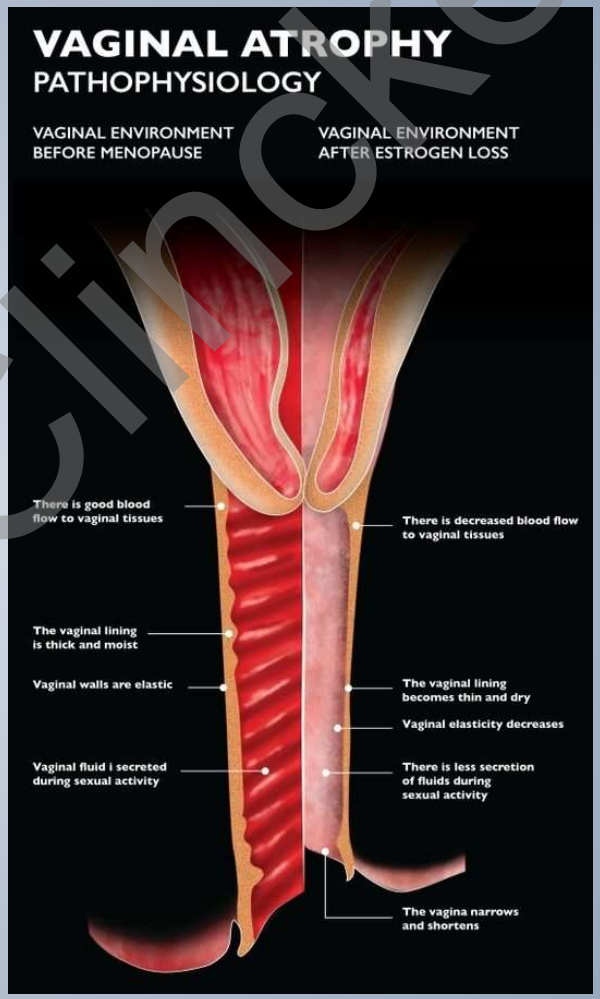
Atrophy

Urinary frequency/ Dysuria/ Stress incontinence due to atrophy and altered pH

↓glycogen → ↓lactobacillus→↑vaginal pH

↓Bartholins gland secretions

THERE ARE FEW CONTRAINDICATIONS TO VAGINAL OESTROGEN !



Symptoms of Menopause: Physical

- Reduced fitness and flexibility
- Altered sleep
- Altered body fat deposition
- Joint and muscle pain

Symptoms of Menopause: Skin & Hair

- ↓sebum→ Dry skin & hair
- ↓skin collagen→ wrinkles
- Reduced nipple sensitivity
- Reduced breast glandular tissue
- Increased pelvic organ prolapse due to reduction in elasticity
- ↓SHBG & ↑Testos:Est → Acne, hirsuitism, hair thinning, male pattern baldness

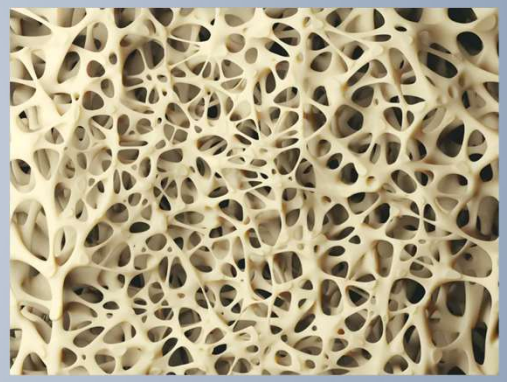
Symptoms of Menopause: Bones

Total ~20% reduction in overall BMD which begins ~12 months prior to menopause and continues for 2-3 years

Osteopenia/Osteoporosis

Increased risk fractures, bone pain

Risk is further increased by smoking



50% of women >60 will suffer an osteoporotic fracture cf 33% of men

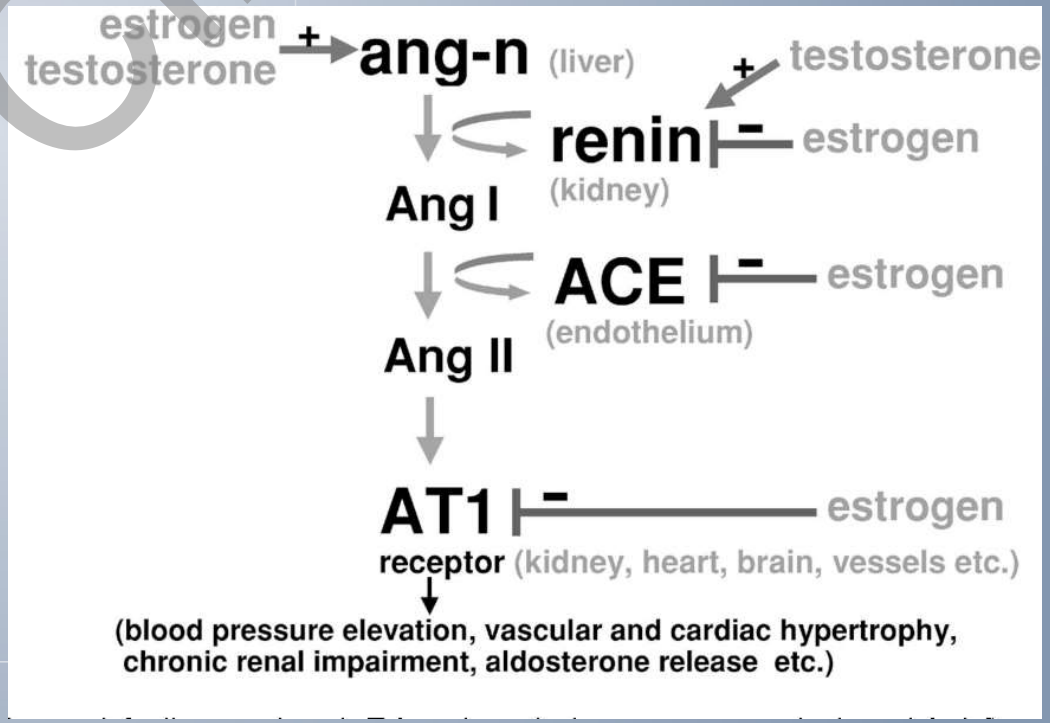
Symptoms of Menopause: Cardiovascular

Reduction of Estrogen levels means

1. loss of negative feedback on the Renin- Angiotensin system
   - Higher BP
   - Vascular and cardiac hypertrophy
   - Chronic renal impairment
   - Aldosterone release

2. Impaired endothelial function
   - Diabetes
   - IHD
   - Stroke
   - Atherosclerosis

3. ↑LDLs ↓HDLs



Symptoms of Menopause: Emotional/cognitive

- "involutional melancholia"
- Increased depression, anxiety and emotional lability
- Feeling of being unloved/unappreciated/irritable
- Insomnia, poor concentration, poor memory, "brain fog"

- ↓ Estrogen→
  - Melatonin fluctuations→ sleep disturbance
  - Vasomotor symptoms→ sleep disturbance→ mood disturbance
  - ↓serotonin receptors→ → mood disturbance

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Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition

P. M. Maki & N. G. Jaff

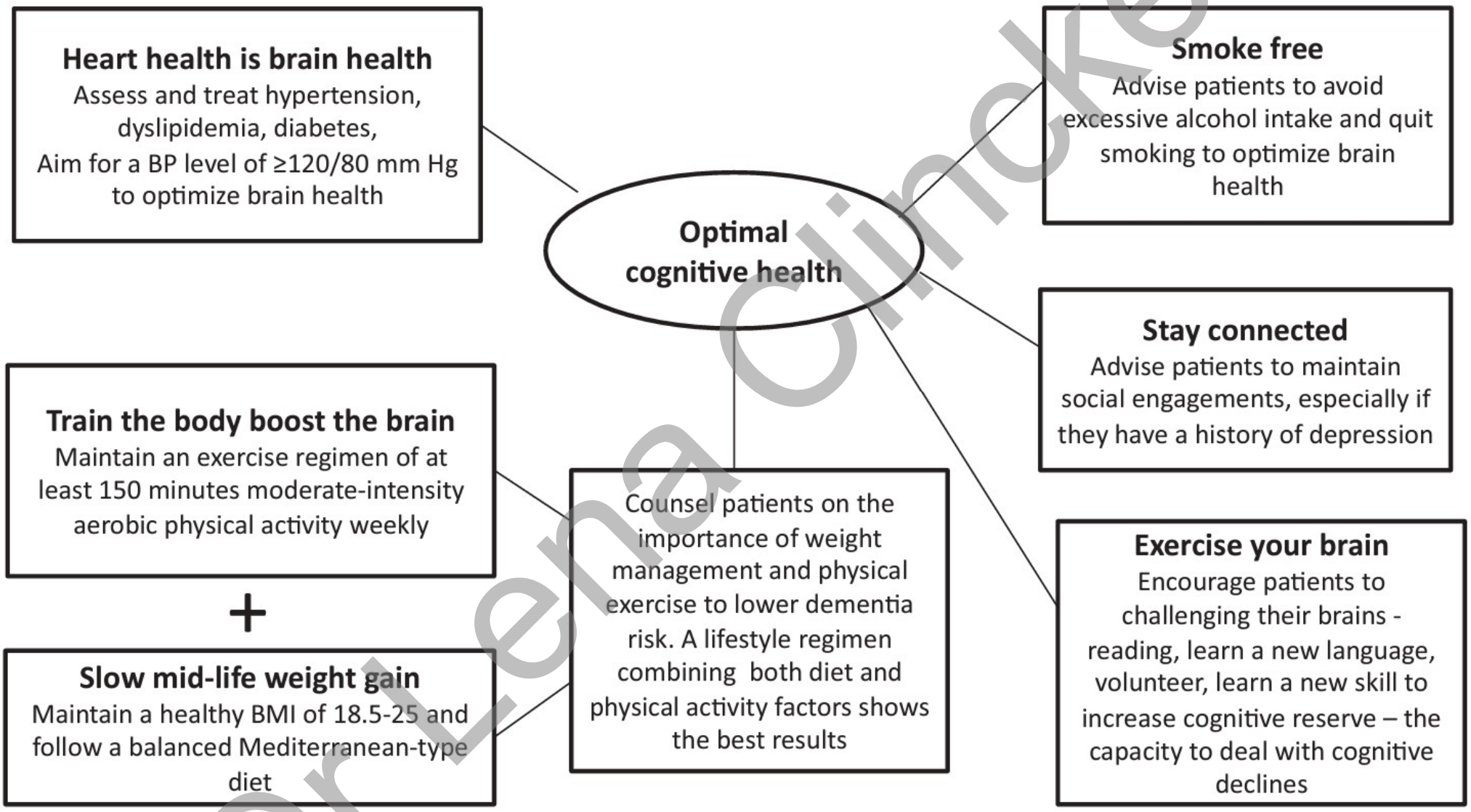
To cite this article: P. M. Maki & N. G. Jaff (2022): Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition, Climacteric, DOI: 10.1080/13697137.2022.2122792

To link to this article: https://doi.org/10.1080/13697137.2022.2122792

Published online: 30 Sep 2022.

Definition of menopause brain fog: the constellation of cognitive symptoms experienced by women around the menopause, which most frequently manifest in memory and attention difficulties and involve such symptoms as difficulty encoding and recalling words, names, stories or numbers, difficulty maintaining a train of thought, distractibility, forgetting intentions (reason for coming into a specific room), and difficulty switching between tasks.

- Brain fog is common at the perimenopause and has been validated in research studies
- Symptoms are troublesome but normal functioning is typically maintained
- No association with Alzheimer's disease
- Uncertain whether hormone therapy improves cognition in perimenopause or for women with troublesome VMS
- Hormone therapy not recommended to treat cognitive symptoms
- Use of hormone therapy for women having early menopause may be protective
- No evidence of harm on cognition by using it even in late post menopause

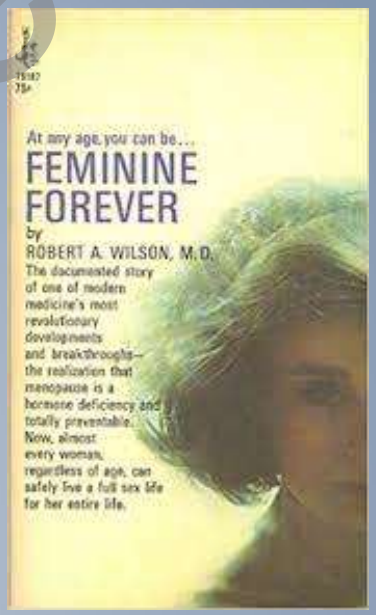


Menopausal Hormone Therapy (MHT)

HRT = MHT

BEFORE THE WHI

- 1940's HRT was first available as Conjugated Equine Estrogen
- Idea that it would render older women youthful and sexy
- Marketed by pharmaceutical company ***Wyeth*** as "the healthy thing to do"
- 1975 – discovered that E alone HRT -> ↑endometrial cancer
- 1990's some observational studies suggested MHT improved QOL, ↓CHD, ↓Osteoporosis, ↓Alzheimers, added 1-2 years life expectancy!!
- 1998 – HERS – 2763 women with documented CHD given E + P → Harm



Robert Wilson 1966


FINANCIAL REVIEW

Hormone alert for cance

More needed to settle HRT scare

HRT linked to cancer and stroke: doctors demand drug restrictions

Expert panel backs HRT cancer warning


Women's Health Initiative

Los Angeles Times- July 10, 2002

Risks of Hormone Therapy Stop Study

port Offers Beating

ROD STEIGER: 1925-2002

Method Actor Infused His Roles With Raw Intensity

Women's Health Initiative – 2002

- First study of its kind – a large multicentre RCT of HRT in "predominantly healthy women"
- Primary outcomes: CHD and invasive breast cancer.
- 2ndry outcomes: stroke, PE, endometrial cancer, bowel cancer, hip fracture and death due to other causes
  - E+P arm (n=16608) (CEE & MPA)
  - E only arm (n= 10739)
  - 2 other arms looking at diet and nutrition

- The combined arm stopped early due to ↑risk breast cancer(OR 1.26)
- The authors concluded that HRT should not be initiated or continued for the primary prevention of CHD

Women's Health Initiative – 2002

	hazard ratio (95% CI)	Relative risk	Absolute risk
CHD events	1.29 (1.02-1.63)	29% increase	7 excess/10 000 women years
strokes	1.41 (1.07-1.85)	41% increase	8 excess/10 000 women years
Pulmonary emboli	2.13 (1.39-3.25)	Two fold increase	7 excess/10 000 women years
Breast cancers	1.26 (1.00-1.59)	26% increase	8 excess/10 000 women years
Colorectal cancers	0.63 (0.43-0.92)	37% decrease	6 fewer/10 000 women years
Hip fractures	0.66 (0.45-0.98)	34% decrease	5 fewer/10 000 women years

Unfortunately results were expressed hazard ratios and "increased risk" making effects appear more extreme than they actually were

OESTROGEN ALONE ARM

- Increased thrombosis risk
- No effect on CAD or bowel cancer
- Increased CVA risk (12/10 000)
- Non-significant *decrease* in breast cancer risk
- 39% decrease fractures

CRITICISM OF WHI

- Average age was 63 (too old)
- Women enrolled had pre-existing health problems:
  - 10% smokers
  - 40% were ex-smokers
  - 70% were overweight or obese
  - 35% were on treatment for HTN
- QOL or resolution of symptoms was not reported. Did these women even have hot flushes?
- Results were exaggerated and presented without context

THE TIMING HYPOTHESIS : CHD

Initiation of HRT within 5-10 years of menopause (closer the better) actually ***decreases*** cardiac events by 39%

However, commencing HRT >10yrs after menopause, increases the risk of cardiac mortality in the first 12 months

THE TIMING HYPOTHESIS : CAD

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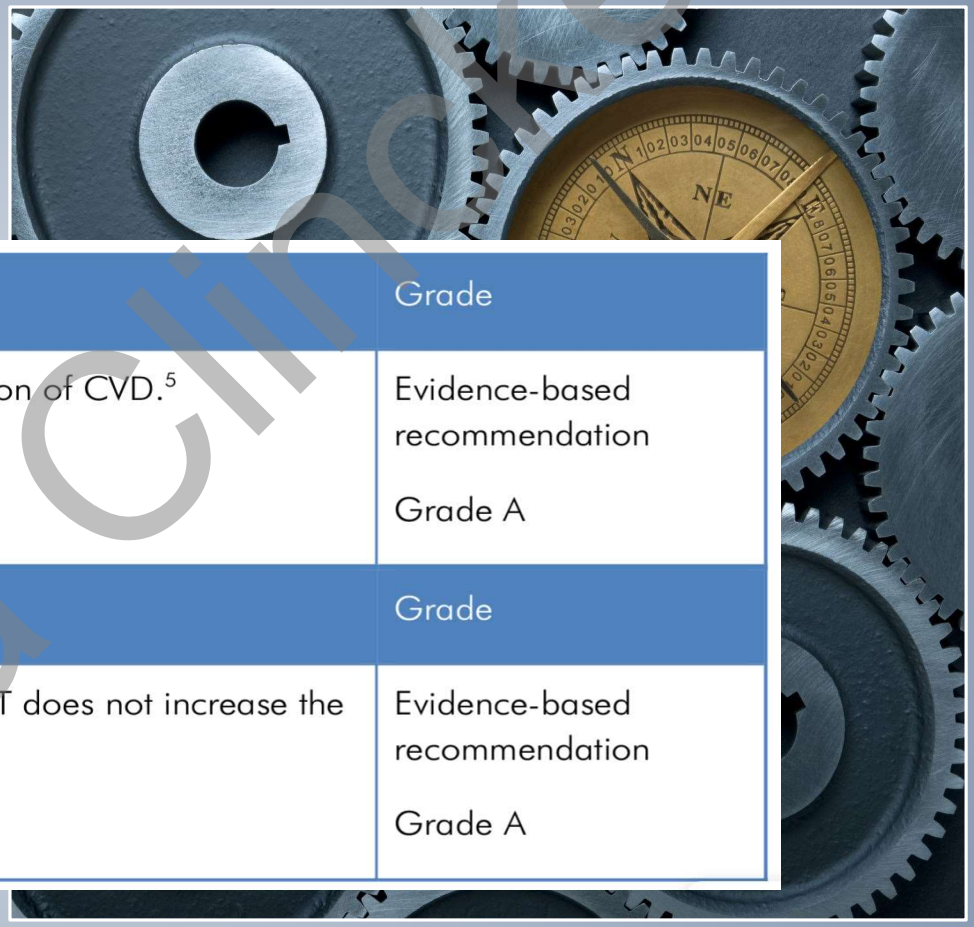

Recommendation 10	Grade
MHT should not be used for the primary prevention of CVD.[5]	Evidence-based recommendation Grade A

Recommendation 11	Grade
In women within 10 years of the menopause MHT does not increase the risk of coronary heart disease.[5]	Evidence-based recommendation Grade A

WHO SHOULD TAKE MHT?

Major indications:

1. **Vasomotor symptoms**
2. Urogenital Symptoms
3. Osteoporosis risk

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Recommendation 5	Grade
The most common indication for the use of MHT is the alleviation of troublesome menopausal vasomotor symptoms.	Consensus-based recommendation

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2. Urogenital Symptoms
3. Osteoporosis risk

Recommendation 5	Grade
The most common indication for the use of MHT is the alleviation of troublesome menopausal vasomotor symptoms.	Consensus-based recommendation

Recommendation 8	Grade
MHT should be considered for symptomatic women who have reduced bone density but have not sustained a fracture[5].	Evidence-based recommendation Grade A

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Many studies on effect on cognition.
Some say the "window of opportunity" exists for cognition as well as for cardiac health
No solid evidence that MHT lowers risk Dementia, however it certainly does not increase the risk (unless commenced >65years)

Mood effects – also controversial

BEFORE PRESCRIBING

History

Examination

Consider BMD (DEXA $)

Pap Smear

Mammogram

Consider endometrial biopsy

WHICH TYPE?

- Bioidentical –
  - Oestradiol (Estrofem – oral, Estradot -patch)
  - Oestrone
  - Oestriol (Ovestin – oral/vaginal)
- Synthetic –
  - Conjugated Equine Estrogen (Premarin)
  - Oestradiol Valerate (Progynova)

WHICH TYPE?

Oral or transdermal?

Transdermal Oestrogen advantages:

- Avoids first pass metabolism by liver
  - Preferred for women with liver disease
  - Women with malabsorption syndromes
  - High risk VTE
  - Migraine with aura
- Better at giving a consistent [Oestrodiol] in bloodstream

A number of studies have failed to show any increased risk VTE with TRANSDERMAL oestrogen

COMBINED - CYCLICAL OR CONTINUOUS?

ALL women with a uterus must have a Progestin alongside the Estrogen

Cyclical recommended for first 12-18 months

- Scheduled bleed
- Helps thin endometrium to a point where continuous will maintain endometrium stability
- Otherwise get BTB
- Exception is Mirena

Continuous or cyclical?

- Use cyclical MHT in the perimenopausal woman or if <12 months since LMP.
- If a woman is >12 months since LMP, can chose continuous

- Bleeding in the first 6 months of MHT use is considered normal and does not need investigation
- Bleeding beyond this → examination, endometrial sampling, ultrasound

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INFORMATION SHEET

AMS Guide to Equivalent MHT/HRT Doses
New Zealand Only

Cyclical oestrogen and progestogen combination MHT

Use cyclical oestrogen and progestogen combinations at peri-menopause or if less than 12 months amenorrhoea

Medium dose		
Trisequens*	tablet	1 and 2mg oestradiol/1mg norethisterone

Continuous oestrogen and progestogen combinations

Should be used if 12 months since LMP or after 12 months cyclical MHT

Low dose		
Product	**Presentation**	**Composition**
Kliovance*	tablet	1mg oestradiol/0.5mg norethistrone
Other Low dose hormonal options		
Livial*, Xyvion*	tablet	2.5mg tibolone
Duavive* (oestrogen/SERM combination)	tablet	0.45mg conjugated equine oestrogens / 20mg bazedoxifene
Medium dose		
Kliogest*	tablet	2mg oestradiol/1mg norethistrone

Progestogen

Suggested alternative doses for use with the oestrogen preparations above where fixed dose therapy is not suitable

Low dose for use with low dose oestrogen		
Product	**Presentation**	**Composition**
Provera (1/2 of 5mg tablet)	tablet	2.5mg medroxyprogesterone acetate
Provera 2.5mg tablet*	tablet	2.5mg medroxyprogesterone acetate
Primolut N (1/4 of 5mg tablet)	tablet	1.25 mg norethisterone
Utrogestan*	capsule	100mg micronised progesterone orally for 25 days out of a 28-day cycle[1] or 200mg orally daily for 12 days out of a 28-day cycle
Mirena* (Pharmac indication for contraception/menorrhagia)	device (5 years)	20mcg/24hrs levonorgestrel

Low dose progestogen-only contraceptive pills (Microlut (30mcg levonorgestrel), and Noriday (350mcg norethisterone) are used by some clinicians in various doses but there is limited data for dosages of these pills required for endometrial protection. 1 mg norethisterone was considered the minimum dose (cyclical or continuous) for adequate endometrial protection in the Cochrane Review (Cochrane Database Syst Rev. 2009 Apr 15;(2):CS000402).

Medium dose for use with medium dose oestrogen		
Product	**Presentation**	**Dose**
Primolut N (1/4 of 5mg tablet)	tablet	1.25 mg norethisterone
Provera, Ralovera	tablet	5mg medroxyprogesterone acetate
Utrogestan*	capsule	100mg micronized progesterone orally 25 days out of a 28-day cycle[1] or 200mg daily for 12 days of a 28-day cycle
Mirena* (Pharmac indication for contraception/menorrhagia)	device (5 years)	20mcg/24hrs levonorgestrel
Higher dose (for use in cyclical therapy or continuous therapy with high dose oestrogen)		
Primolut N (1/2 5mg tablet)	tablet	2.5mg norethisterone
Provera, Ralovera	tablet	10mg medroxyprogesterone acetate
Utrogestan*	capsule	200mg orally daily for 12 days out of a 28-day cycle[1]. Safe continuous dose unknown due to insufficient data.
Mirena* (Pharmac indication for menorrhagia/anaemia)	device (5 years)	20mcg/24hrs levonorgestrel

[1]Can be used daily if compliance is an issue.

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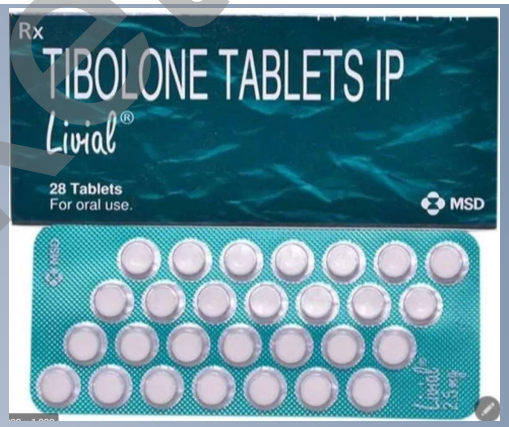
Oestrogen only therapy:

Only use these if patient has had a hysterectomy or in combination with a progestogen or Mirena if intact uterus

Low dose		
Product	**Presentation**	**Composition**
Estrofem*	tablet	1mg 17 B oestradiol
Progynova	tablet	1mg oestradiol valerate
Premarin*	tablet	0.3mg conjugated equine oestrogen
Estradot 25	transdermal patch	25 or 37.5mcg/24hrs 17B oestradiol (twice weekly application)
Climara 25*	transdermal patch	25mcg/24hrs 17B oestradiol (weekly application)
Estrogel*^	gel	0.75mg oestradiol = 1 pump
Medium dose		
Progynova	tablet	2mg oestradiol valerate
Estradot 50	transdermal patch	50mcg/24 hours 17B oestradiol (twice weekly application)
Premarin*	tablet	0.625mg conjugated equine oestrogens
Sandrena*#	gel	1mg oestradiol (daily application)
Climara 50*	transdermal patch	50mcg/24hrs 17B oestradiol (weekly application)
Estrogel*^	gel	1.5mg oestradiol = 2 pumps
High dose		
Estradot 75 Estradot 100	transdermal patch	75 or 100mcg/24 hours (twice weekly application)
Climara 75*	transdermal patch	75mcg/24hrs 17B oestradiol (weekly application)
Climara 100*	transdermal patch	100mcg/24hrs 17B oestradiol (weekly application)
Estrogel*^	gel	2.25mg oestradiol = 3 pumps or 3.0mg oestradiol = 4 pumps

TIBOLONE (LIVIAL)



- Synthetic STEAR
- Androgenic, Progestogenic, Estrogenic components
- Slighter less effective for vasomotor Sx than Oestrogen
- Less breast tenderness & less breast density than with MHT
    - LIBERATE study showed increased risk recurrence breast cancer OR 1.5 (1.21-1.85)
- Much lower risk VTE
- LIFT study showed Tibolone increased risk stroke (OR 2.3) *cf MHT- 1.41*
- LIFT study also concluded a reduction in vertebral fractures by 50%
- May be good for libido and energy levels

DUAVIVE = Bazedoxefine + Conjugated equine estrogens

- Bazedoxefine is a SERM
- Combined with CEE is a Tissue Selective Estrogen Complex (TSEC)
- Prevention of osteoporosis, management of menopausal Sx w/o need for Progestin
- More effective than placebo, less effective than MHT but less bleeding & breast tenderness than MHT
- SE: abdo pain, GI symptoms, vv thrush, ↑triglycerides

WHAT ARE THE CONTRAINDICATIONS?

Oestrogen dependent Cancers-

- breast cancer
- endometrial cancer

High risk VTE

- Thrombophilia
- Previous VTE
- Smokers

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Recommendation 9	Grade
Oral MHT is contraindicated in women with previous a personal history of venous thromboembolism (VTE).[5]	Evidence-based recommendation Grade A

WHAT ARE THE CONTRAINDICATIONS?

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- breast cancer
- endometrial cancer

High risk VTE

- Thrombophilia
- Previous VTE while on HRT/COCP
- Smokers

Recommendation 9	Grade
Oral MHT is contraindicated in women with previous a personal history of venous thromboembolism (VTE).[5]	Evidence-based recommendation Grade A

CAUTION

- Significant liver disease
- Undiagnosed vaginal bleeding
- Uncontrolled HTN
- >60yrs />10 yrs since menopause

Recommendation 13	Grade
Due to the increasing risk of breast cancer with duration of MHT, annual review of use is recommended. Continuation beyond 5-7 years should be based on an individual woman's needs with regards to the benefits and risks of continued MHT.[5]	Consensus -based recommendation

REMEMBER MHT IS NOT A CONTRACEPTIVE!

Perimenopausal women should stay on contraception for 12 months after LMP

If menopause occurs <50yrs, it is recommended they stay on it for 2 years

If a woman is amenorrhoeic because of a Progestin contraceptive, can test FSH.

If FSH >30, continue for 12 months, then stop

If FSH <30, continue for12 months then test again.

Estrogen based contraceptives and Depot Provera not recommended >50yrs.

The oldest woman to conceive spontaneously was 59!!!!

WHAT ARE THE ALTERNATIVES TO MHT? …FOR VMS

Pharmacological

- Clonidine – 40% reduction in VMS at dose 25-50mg BD (cf placebo – 30%)
- High dose Progestagens – Provera used at 10-20mg/day but SE common and may hasten bone loss over time
- Gabapentin/Pregabolin – 50-65% reduction in VMS
- **Venlafaxine – at low dose, has been proven similar efficacy as Oestrogen for relief VMS**

SSRIs for VMS

- Venlafaxine
  - SNRI and also a weak Dopamine reuptake inhibitor
  - Better at treating VMS when used at a *lower* dose (75mg/day)
- Desvenlafaxine – may work for longer
- Escitalopram
  - 10-20mg/day is effective treatment for VMS and Depression
  - Less negative effect on sexual Fn
  - Less withdrawal Sx when ceased
- Fluoxetine/Sertraline/Citalopram
  - Not as efficacious
  - May worsen Br cancer outcomes in Tamoxifen users

Bone Mineral Density

Raloxifene (SERM)

- 50% ↓ vertebral fractures (no effect of peripheral fractures)
- ↓ Estrogen effects on breast (and on uterus)
- No risk on CHD
- Increase risk VTE (same as MHT)
- Protective effect on bones finishes as soon as drug is stopped

Bisphosphonates – Alendronate

- Inhibition of Osteoclasts
- ↓ risk vertebral fractures by 50%
- Effects on bone continue years after ceasing
- SE – Osteonecrosis jaw, GI upset

Raloxifene & Alendronate are more effective at improving BMD when used in combination

VAGINAL SYMPTOMS

- Oestrogen cream- very few contraindications. Systemic absorption minimal
  - Does not require use of Progestogen for endometrial protection
- Lubricants (Silicone better than water based)
- fractional CO2 laser treatment
  - 1-3 treatments
  - Need repeat every 6-12 months
  - More evidence required

WHAT ARE THE ALTERNATIVES TO MHT? ....ALTERNATIVE

Lydia Pinkham's vegetable gum

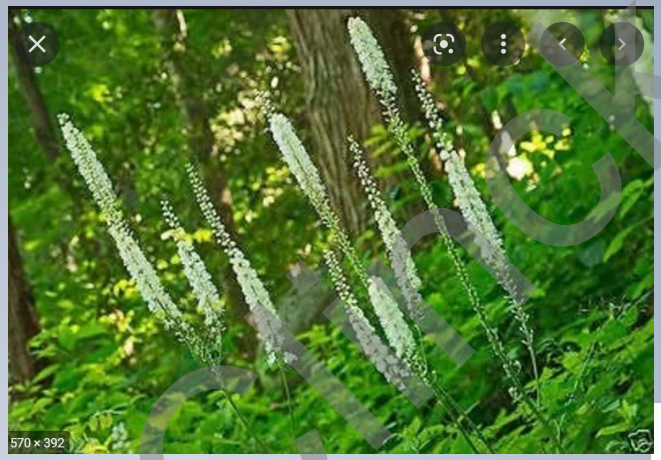
Phytoestrogens/Isoflavins

Red Clover

Wild Yam

Black Cohash (Remifemin)

- 1-2 tabs BD
- Several small studies have shown benefit but likely mild (↓VMS)
- Good quality profile in terms of manufacturing
- Often used with Hypericum (St Johns wart) and the combination has been shown to improve VMS and mood Sx.



Is it Premature menopause?
This is a treatable disease

Premature/early menopause?

- POF (premature ovarian failure)
- Cessation of menses prior to 45
- Surgical menopause
  - Bilateral Oophorectomy for cancer, endometriosis, Prophylaxis (BRCA1/2)
- Medical menopause

    - radiation therapy to pelvis/brachytherapy

Premature Menopause – please give them Estrogen!!

…till ***at least*** 50 (average age of menopause is 51)

Without Estrogen these women are at increased risk of-

- osteoporosis (↑by 5X)
- CV disease (↑by 450X)
- Cognitive impairment
- Earlier death

Premature Menopause – please give them Estrogen!!

…till ***at least*** 50 (average age of menopause is 51)

Recommendation 6	Grade
Women with premature (less than 40 years) or early (less than 45-years) menopause should be offered MHT at least until aged 50 years unless otherwise contraindicated.[5]	Evidence-based recommendation Grade B

- Cognitive impairment
- Earlier death

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Will need a higher dose of Estrogen!

What about Testosterone replacement?

- There is no Menopause associated Testosterone deficiency
- Actually an age related decline that starts much earlier and continues gradually for many years
- Sexual function is complex
  - Relationship
  - Mental health
  - General health
  - Estrogen deficiency
- Evidence that sexual function declines with falling Estrogen Not falling Testosterone

What about Testosterone replacement?

- Check levels of Testosterone prior to commencing to ensure deficient (although unreliable).
- Check Testosterone levels 6 weeks after initiation and then every 6 months thereafter to ensure no over-dosing.
- Will cause ↓HDLs, consider checking lipid profile

- Really only indicated for women who have had ovaries removed.

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