Current controversies with HRT over the last decade

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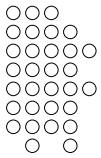


1999 Management of the Menopause The handbook of the British Menopause Society eds Rees M and Purdie DW

- Acute Benefits
- Relief of vasomotor symptoms
- Relief of psychological symptoms
- Long Term Benefits
- Maintains bone mass
- May reduce the risk of cardiovascular disease
- Reduces problem associated with urogenital and connective tissue atrophy
- May reduce risk or delay the onset of Alzheimer's disease
- May reduce the incidence of colon cancer
- May reduce tooth loss
- May reduce adult onset macular degeneration and cataract formation
- May improves balance and reduce falls
- May improve wound healing

1999 Management of the Menopause The handbook of the British Menopause Society eds Rees M and Purdie DW

- Risks
- Breast cancer
- VTE
- Endometrial cancer

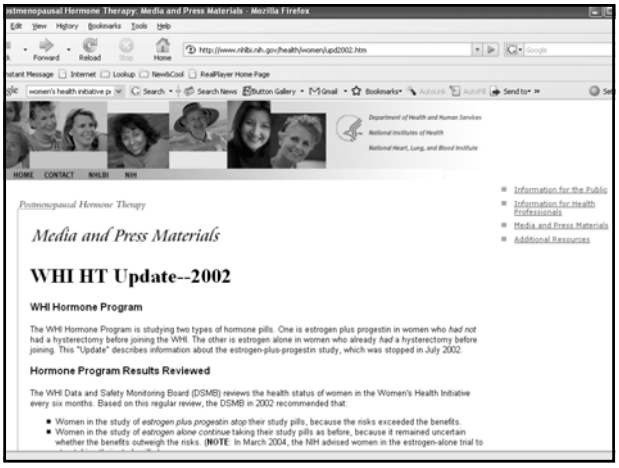
WHI studies: RCT and OS

- Designed 1991-2
- Postmenopausal women ranging in age from 50 to 79 years were enrolled into either a clinical trial (CT) that would eventually include 68,132 women (mean age 63 years), or an observational study (OS) that would involve 93,676 women. The WHI Extension Study is following up 115,400 participants from each of the original WHI study components until 2010.
- The randomised CT evaluated three distinct interventions:
- 1] a low-fat eating pattern (n=48,835)
- 2] hormone replacement therapy (HRT)
- CEE 0.625mg for hysterectomised women (n=10,739),
- CEE 0.625mg and MPA 2.5mg for women with a uterus (n=16,608),
- 3] calcium and vitamin D supplementation (n=36,282).
- If eligible, women could choose to enroll in one, two, or all three of the randomized trial components.

Million Women Study:OS

- 1,084,110 women surveyed 1996-2000
- 75- 83% women invited to have mammogram accept
- 71% screened women surveyed
- 66 centres
- Baseline questionnaire for HRT use
- Follow up 2.6 years
- Outcomes include: breast cancer, endometrial cancer, ovarian cancer, gallbladder disease

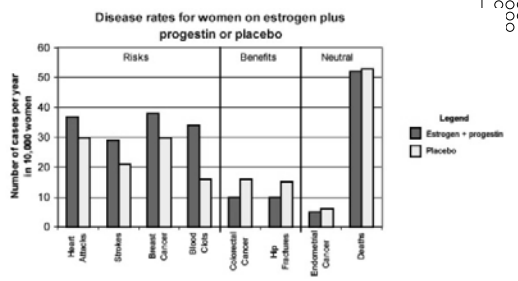
Million Women Study Collaborators 2002, 1999
Banks et al 2002, NHSBSP Statistics



Postmenopausal Hormone Therapy

Media and Press Materials WHI HT Update--2002

- WHI Hormone Program Hormone Program Results Reviewed
- The WHI Data and Safety Monitoring Board (DSMB) reviews the health status of women in the Women's Health Initiative every six months. Based on this regular review, the DSMB in 2002 recommended that:
- * Women in the study of estrogen plus progestin stop their study pills, because the risks exceeded the benefits.
- * Women in the study of estrogen alone continue taking their study pills as before, because it remained uncertain whether the benefits outweigh the risks.
- http://www.nhlbi.nih.gov/health/women/upd2002.htm



Mail Online

- **Combined HRT users `at risk of cancer` 8 August 2003**
-
- Doctors and GPs' surgeries across Britain have received advice on how to reduce panic among women taking hormone replacement therapy after a massive study revealed a significantly increased risk of breast cancer.
- Researchers found that using the combined oestrogen-progestagen treatment - the most common form of HRT - doubled women's risk of developing breast cancer compared with those not taking HRT.
- The Million Women Study also confirmed an increased risk of 45% for users of tibolone and 30% among those using oestrogen-only HRT.
- About 1.5 million women in the UK are currently using HRT, with about half that number taking the combination treatment.
- The Committee on Safety of Medicines (CSM), which advises the Government on the quality of drugs, has provided advice to all healthcare professionals in light of the research.
- The Government is keen for women not to panic, saying they should make a routine appointment to discuss their treatment with their doctor.
- The CSM is urging GPs to assess each case individually and says the study's results "do not necessitate any urgent changes to women's treatment".
- But one Dutch researcher, writing alongside the results of the study published in The Lancet, said women should "discontinue HRT use as soon as possible".

The media and HRT

- Wall Street Journal 11 Jul 2007

According to the Journal, in the five years since the study was released, many in the medical community have said "some aspects" of the initial findings "were either misleading" or "overgeneralized in large part because they excluded many of the study's own investigators and physicians from the first review".

- According to the Journal, the WHI's 40 researchers in 2002 were told 11 days before the initial WHI study report in JAMA was released that it had been halted early. Although some of them were concerned that the results were "too broadly interpreted," it was "too late to make meaningful changes" to the JAMA article, the Journal reports.
- Robert Langer -- "I think that had the initial report been written by a broader group, as almost all of our later papers have been, it would have been framed differently."
- According to the Journal, key questions about long-term use of HRT are "far from resolved." According to the health care information company IMS Health, HRT sales have declined 30% since the WHI results were published in 2002 (Wall Street Journal, 7/9).

The media and HRT

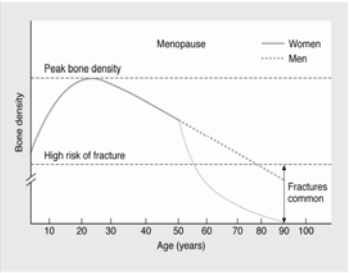
- HRT scares 'have caused suffering for millions' Daily Telegraph 9 October 2007
- Was the promotion of HRT as an '*elixir of life'* a triumph of marketing over science? What is the truth about HRT? Complicated. The Times 8 March 2008

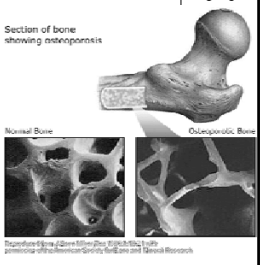
Issues

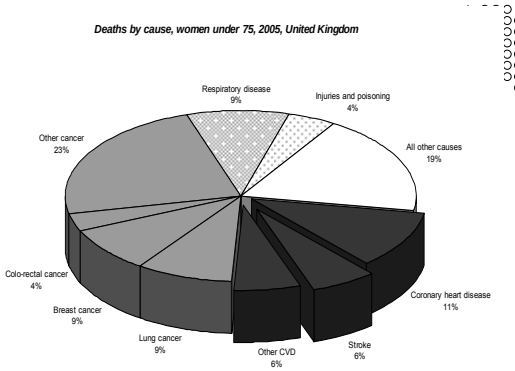
- Menopausal symptoms: vasomotor, urogenital
- Osteoporosis
- Cardiovascular disease
- Dementia
- Breast cancer
- Premature menopause
- Sexual dysfunction

Hot flushes

Osteoporosis affects 1 in 3 women







Office of National Statistics (2006)
Scotland, General Register Office (2006)
Northern Ireland, General Register Office (2006)

www.heartstats.org

Dementia

- Worldwide about 25 million people have dementia, with 4.6 million new cases of dementia every year (one new case every 7 seconds).
- It is estimated that the number of people affected will double every 20 years to 81.1 million by 2040.
- Its prevalence and incidence increases with age and the risk of developing dementia doubles every five years after age 65. Only about 1-2% of people aged 65 years are affected, increasing to at least 20% in people aged 80 years and over. It may exceed 50% in those over 90.
- The average life expectancy of a person with dementia is 3–7 years after diagnosis
- Dementia causes significant distress to patients, their carers and families and has an enormous impact on society.

Female sexual dysfunction:Consensus Classification System (adapted from Basson et al 2000)

Sexual Desire Disorders
Hypoactive sexual desire disorder (HSDD)
Sexual aversion disorder (SAD)
Sexual Arousal Disorders
The persistent or recurrent inability to attain
or maintain sufficient sexual excitement,
Causing personal distress
Orgasmic Disorder
The persistent or recurrent difficulty, delay in,
or absence of attaining orgasm after
sufficient sexual stimulation and arousal,
which causes personal distress.

Sexual Pain Disorders
Dyspareunia
Vaginismus
Noncoital sexual pain disorders –

Each of the categories is subtyped, as:
- Lifelong vs acquired.
- Generalised vs situational.
- Aetiology (organic, psychogenic, mixed, unknown)

FSD affects 43% women aged 57-85 years.
Lindau et al. N Engl J Med 2007;357:762-74.

HRT February 2008 BMS consensus statement http://www.thebms.org.uk

- **Benefits**
- Menopausal symptoms
- Osteoporosis
- Colorectal cancer

- **Risks**
- Breast cancer
- Endometrial cancer
- VTE
- Gall bladder disease

- **Uncertainties**
- Cardiovascular disease
- Dementia/ Alzheimers
- Ovarian cancer
- Quality of life

Menopausal symptoms

- **Vasomotor symptoms**
  There is good evidence from randomised placebo-controlled studies, that oestrogen is effective in treating hot flushes and improvement is usually noted within 4 weeks. Relief of vasomotor symptoms is the commonest indication for HRT prescription and is often used for less than 5 years.
- **Urogenital symptoms**
  Vaginal dryness, soreness, superficial dyspareunia, and urinary frequency and urgency respond well to oestrogens. Improvement may take several months. Long term treatment is often required.

  Sexuality may be improved with oestrogen alone but may also need testosterone addition, especially in young oophorectomised women.

Osteoporosis

- Reduces risk of osteoporotic fractures at both spine and hip
- RCT evidence
- Bone sparing dose estradiol 2mg, conjugated equine estrogens 0.625mg and transdermal 50mcg patch.
- But half these doses or even lower also conserve bone mass
- Continuous and life long use is required.
- However a few years treatment with HRT around the time of menopause may have a long term effect on fracture reduction.
- Estrogen is the best option, particularly in younger (less than 60 years and/ or symptomatic women.
- The initiation of " standard dose" HRT is not recommended solely for fracture prevention in women over 60.

British Menopause Society Consensus statement Oct 2007
http://www.thebms.org.uk. Menopause International: 13;178-181

Colorectal cancer

- Reduced risk
- No evidence in high risk populations

Breast cancer

- HRT confers same degree of risk as late natural menopause (2.3% compared with 2.8% per year respectively)
- Breast cancer risk falls after cessation of use, risk being no greater than that in women who have never been exposed to HRT by 5 years.
- Increased risk of breast cancer with longer-term exposure is mainly limited to lean women (ie, BMI<25kg/m2).
- No increased risk breast cancer in women taking HRT for a premature menopause under age 50

Factors that increase the relative risk of breast cancer in women

Relative risk	Factor
RR >4.0	Age 65 vs <65 Inherited gene mutations BRCA1/2 Two or more first degree relatives diagnosed with breast cancer at an early age
RR 2.1-4.0	One first degree relative with breast cancer atypical hyperplasia
RR 1.1-2.0	Early menarche/late menopause Nulliparity/first pregnancy after 35 HRT Obesity Alcohol consumption Being tall Eating grapefruit/red meat

From American Cancer Society
Breast Cancer Facts & Figures 2007-2008

Breast cancer risk per 1,000 women on intention to treat analysis of 5 years from the Women's Health Initiative studies (HR = hazard ratio, CI=confidence interval) (Chlebowski et al 2003)

	Oestrogen only		Continuous Combined HRT	
	HR (95% CI)	Difference	HR (95% CI)	Difference
50-59 years	0.72 (0.43-1.21)	-4 (-7 to +3)	1.20 (0.80-1.82)	+3 (-3 to +11)
60-69 years	0.72 (0.49-1.07)	-5 (-9 to +1)	1.22 (0.90-1.66)	+4 (-2 to +12)
70-79 years	0.94 (0.56-1.60)	-1 (-9 to +12)	1.34 (0.88-2.04)	+7 (-2 to +21)
Overall	0.77 (0.59-1.01)	-4 (-7 to 0)	1.24 (1.01-1.54)	+4 (0 to +9)

Endometrial cancer risk and HRT after 5 or more years of use.

Type	OR
oestradiol alone	6.2 (95% CI 3.1-12.6)
conjugated oestrogens	6.6 (95% CI 3.6-12.0).
cyclic use of progestogens plus oestrogen i.e., fewer than 16 days per cycle (most commonly 10 days)	2.9 (95% CI 1.8-4.6)
continuous progestogen use along plus oestrogens	0.2 (95% CI 0.1-0.8)

• OR= odds ratio
CI= confidence interval
Weiderpass et al 1999

Endometrial cancer

- WHI no increase risk endometrial cancer with continuous combined therapy
- MWS 'Oestrogens increase the risk of endometrial cancer. Progestogens counteract the adverse effect of oestrogens on the endometrium, the effect being greater the more days every month that they are added to oestrogen'.
- Long cycle HRT ? Erkkola et al. J Br Menopause Soc 2004;10:9-13.
- National Institutes of Health-AARP Diet and Health Study cohort In 51,312 women who never used hormones or only used estrogen-plus-progestin regimens at doses consistent with current practice, neither sequential estrogen plus progestin (daily estrogen plus progestin for 10-14 days per cycle) nor continuous estrogen plus progestin (daily estrogen plus progestin for >/=20 days per cycle) had any statistically significant association with endometrial cancer. Lacey et al Cancer 2007;109:1303-11.

HRT and VTE (WHI)

- Combined HRT VT risk increased (HR 2.06; 95% CI, 1.57-2.70).
- Risk increases with age
- Risk increases in overweight and obese women
- Factor V Leiden enhanced the hormone-associated risk of thrombosis 6.69-fold
- Other genetic variants (prothrombin 20210A, methylenetetrahydrofolate reductase C677T, factor XIII Val34Leu, PAI-1 4G/5G, and factor V HR2) did not modify the association of hormone therapy with venous thrombosis.
- Estrogen alone An early increased VT risk is associated with use of estrogen, especially within the first 2 years, but this risk increase is less than that for estrogen plus progestin (HR 1.32; 95% CI, 0.99-1.75). There were no significant interactions between estrogen use and age, body mass index, or most other VT risk factors.

Transdermal versus oral estrogen

- Meta-analysis of observational studies showed that oral oestrogen but not transdermal oestrogen increased the risk of VTE.
- The risk of VTE in women using oral oestrogen was higher in the first year of treatment (4.0, 2.9 to 5.7) compared with treatment for more than one year (2.1, 1.3 to 3.8; P<0.05).
- No noticeable difference in risk of VTE was observed between unopposed oral oestrogen (2.2, 1.6 to 3.0) and opposed oral oestrogen (2.6, 2.0 to 3.2).

- Canonico et al Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008 31;336:1227-31.

HRT and gall bladder disease

- WHI The annual incidence rate for any gallbladder event was:
- 78 events per 10 000 person-years for the CEE group (vs 47/10 000 person-years for placebo)
- 55 per 10 000 person-years for E + P (vs 35/10 000 person-years for placebo).
- MWS Transdermal estrogen confers lower risk than oral estrogen

Coronary heart disease per 10,000 women per year

- Combined HRT
- The excess absolute risk at
- 50-59 + 5
- 60-69 +1
- 70-79 + 23

- Oestrogen alone HRT
- The reduced absolute risk at
- 50-59 - 10
- 60-69 years -5
- with an excess risk at 70-79 + 4

Years since menopause and starting HRT

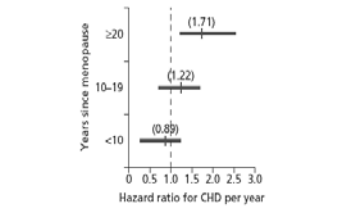


Figure 7.1 Influence of time since menopause on the effect of hormone replacement therapy on coronary heart disease. Adapted from Manson (2003)

Coronary heart disease per 10,000 women per year WHI combining both arms

- Absolute risk at
- 50-59 -2
- 60-69 -1
- 70-79 + 19

Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-77.

Randomized controlled trials of HRT as secondary prevention for coronary heart disease.
CEE=conjugated equine estrogens.
MPA=medroxyprogesterone acetate.

Study	Hormone replacement therapy	Route	Relative risk (95% confidence interval) of acute myocardial infarction	N
HERS (Hulley, 1998)	CEE/MPA	Oral	0.99 (0.8 to 1.22)	2769
PHASE (Clarke, 2002)	17β-oestradiol	Patch	1.29 (0.84 to 1.95)	255
WEST (Viscoli, 2001)	17β-oestradiol	Oral	1.1 (0.6 to 1.9)	664
ESPRIT (Cherry, 2002)	Oestradiol valerate	Oral	0.99 (0.7 to 1.41)	1017

Stroke cases per 10,000 women per year.

- Combined HRT
- Excess absolute risk at 50-59 + 4
- 60-69 + 9
- 70-79 + 13

- Oestrogen alone HRT
- Excess absolute risk at 50-59 0
- 60-69 +19
- 70-79 +14

Stroke cases per 10,000 women per year WHI combined trials.

- Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56).
- Risk did not vary significantly by age or time since menopause.

Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007;297:1465-77.

A mechanistic answer

- The cardioprotective effects of estrogen are mediated by receptors expressed in vascular cells.
- 27-hydroxycholesterol (27HC), an abundant cholesterol metabolite that is elevated with hypercholesterolemia and found in atherosclerotic lesions, is a competitive antagonist of estrogen receptor action in the vasculature.
- As well as antiestrogenic effects, there were proestrogenic actions of 27HC that were cell-type specific, indicating that 27HC functions as an endogenous selective estrogen receptor modulator (SERM).
- 27HC is a contributing factor in the loss of estrogen protection from vascular disease.

- Umetani et al. 27-Hydroxycholesterol is an endogenous SERM that inhibits the cardiovascular effects of estrogen.
- Nat Med. 2007; 13:1185-92.

Dementia and cognition

- WHI found a two-fold increased risk of dementia in women with both oestrogen and progestogen and oestrogen alone. However, this increased risk was only significant in the group of women over the age of 75 years.
- WHI found deterioration in cognitive function in women aged over 65, especially in those with lower cognitive function at the initiation of treatment.
- There may be a window of opportunity in the early postmenopause when the pathological processes are being initiated.

Ovarian cancer

- Affects 7,000 women in UK per year
- Most important risk factors are increasing age and BRCA1/2 gene mutations
- Results contradictory
- Combined HRT versus estrogen alone
- MWS both E alone and combined HRT increased risk, WHI no increased risk with combined HRT
- No increase risk in BRCA1 carriers

Quality of life

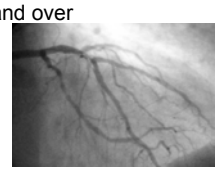
- May improve
- Confounders relief of menopausal symptoms
- WISDOM study: Hot flushes were experienced in the combined HRT and placebo groups by 30% and 29% at trial entry and 9% and 25% at one year, respectively.

- **MENQOL** Menopause-specific Quality of Life Questionnaire
- **MRQ** Menopause Representations Questionnaire
- **MRS** Menopause Rating Scale
- **UQOL** Utian Quality of Life scale
- **WHQ** Women's Health Questionnaire

Welton AJ, et al ; WISDOM team..Health related quality of life after combined hormone replacement therapy: randomised controlled trial. BMJ. 2008 Aug 21

Premature menopause

- POF increases risk CVD, osteoporosis, dementia, cognitive decline, parkinsonism
- Need HRT/estrogen until average age of menopause ie 52
- This does not increase breast cancer risk compared to that found in normally menstruating women
- Advice unchanged by WHI and MWS since both undertaken in women aged 50 and over
- CSM Dec 2003



- Ewertz et al. Br J Cancer 2005; 92:1293-7.
- Rocca et al. Neurology. 2007; 69:1074-83.
- Rocca WA et al. Neurology. 2008; 70:200-9.

Premature menopause

- Jones GL, Ledger W, Mitchell C. Suspected premature menopause. *BMJ* 2008;336:833. (12 April.)
- Lewars MD.Premature menopause: Article's recommendation of HRT is highly questionable. BMJ. 2008 May 10;336(7652):1033-4.

  'it seems irresponsible for Jones et al to recommend combined hormone replacement therapy for 15 years or more'
- Rees MC.Premature menopause: Hormone replacement therapy is indeed indicated. BMJ. 2008 May 24;336(7654):1148.

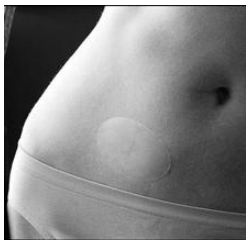
Letters
Hormone replacement therapy
HRT in premature menopause

- Grant's blanket statement,1 based on the WISDOM study,2 that "it would be irresponsible to think that any use of hormone replacement therapy (HRT) is justifiable" will confuse those dealing with women with early ovarian failure in their 20s and 30s. National guidelines recommend the use of HRT in this group until the average age of the natural menopause in the early 50s.3 The results of the WISDOM study, which randomised women with a mean age of 63.8 years, should not be extrapolated to them.
- **Cite this as:** *BMJ* 2008;337:a1668
- **Margaret C P Rees**,

- **References**
- 1. Grant ECG. Hormone replacement therapy: Irresponsible to modify current guidelines *BMJ* 2008;337:a1494. (3 September.)
- 2. Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al, for the WISDOM team. Health related quality of life after combined hormone replacement therapy: randomised controlled trial. *BMJ* 2008;337:a1190. (21 August.)
- 3. British Menopause Society. BMS consensus statements: summary and practice points. Premature menopause.

Testosterone patch (Intrinsa)

- Testosterone is produced by the ovaries and adrenal glands; it is linked to female sexual function.
- Oophorectomy results in an immediate decline in testosterone.
- The loss of sexual desire can be associated with this testosterone drop.
- Intrinsa (testosterone) transdermal patch 300 mcg/24hours is now licensed for the treatment of hypoactive sexual desire disorder in bilaterally oophorectomised and hysterectomised women receiving concomitant oestrogen therapy.
- Also effective in naturally menopausal women.



Shifren et al Menopause. 2006;13:770-9.
Davis et al Menopause. 2006;13:387-96.

Where are we now

- Differences between regimens (E v E+P)
- Timing
- Duration of use
- Should not be used for the first time in women over 60
- Premature menopause
- Dose: one size does not fit all
- Route: oral v transdermal
- Place and safety of alternative treatments:
  standard pharmacopoeia for symptoms and osteoporosis,
  complementary and alternative medicines