

여성갱년기 환자에서 여성호르몬의 새로운 접근법

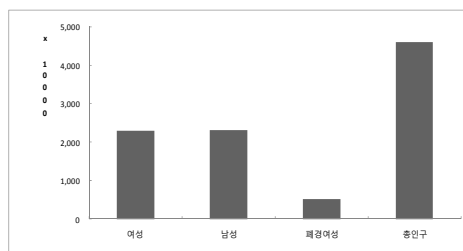
박 셋 별
아주의대 가정의학과

Contents

- General Consideration
- Clinical Symptoms
- Evaluation
- Treatment
- Summary

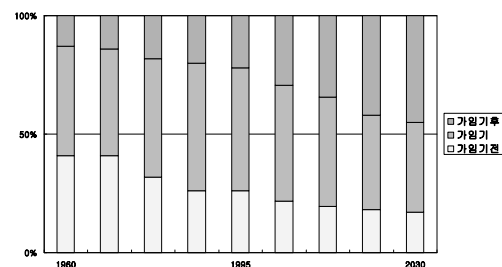
General consideration

연령별 인구자료



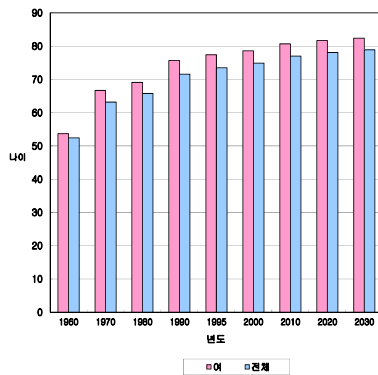
통계청 2011

여성 인구 분포의 변화

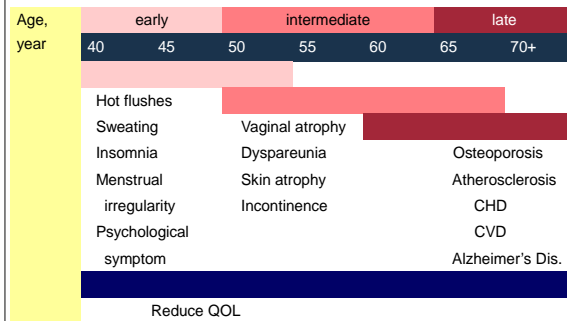




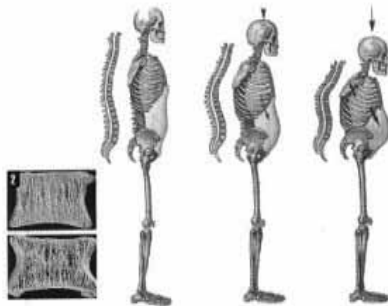
평균 수명



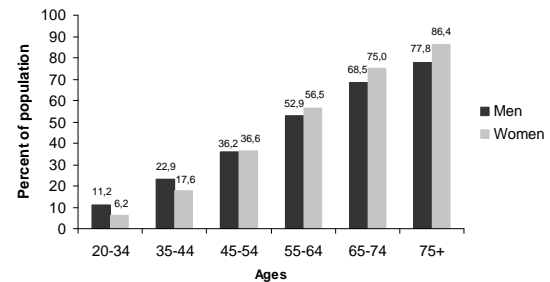
Symptom of menopause



골다공증 (Osteoporosis)



성별, 연령에 따른 심혈관질환의 발생률



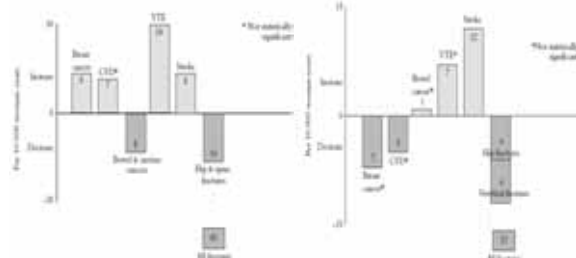
HRT

Benefits	Risks
Vasomotor symptoms	Breast Cancer
Urogenital Symptoms & Sexual function	VTE
Osteoporosis	Stroke
Colon Cancer	Endometrial cancer
Uncertainties	
Cardiovascular disease	
Alzheimer's disease	
Ovarian cancer	
Quality of life	

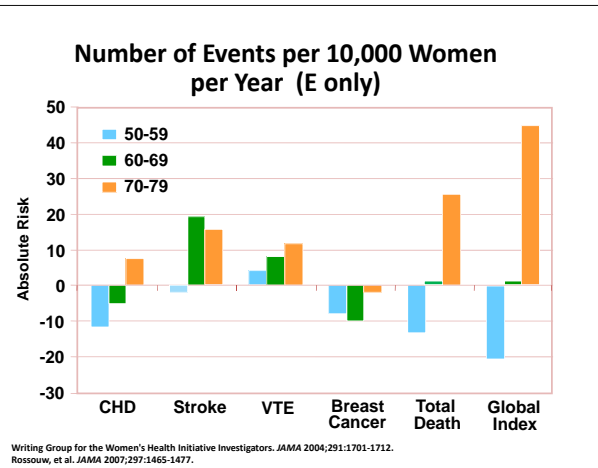
British Menopause Society Consensus Statement www.thebms.org.uk

WHI, WHI, WHI ?

5.2 years of combined hormone (EP) therapy 7 years of estrogen-only hormone therapy



(MacLennan et al., Climacteric 2004)

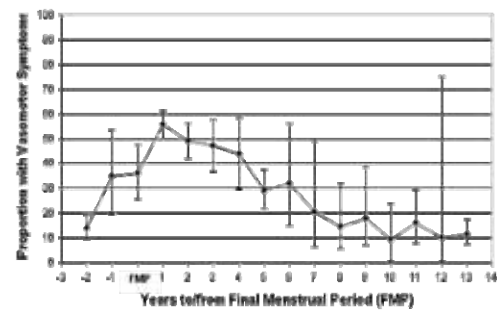


Clinical Symptoms



열성 홍조

How long?

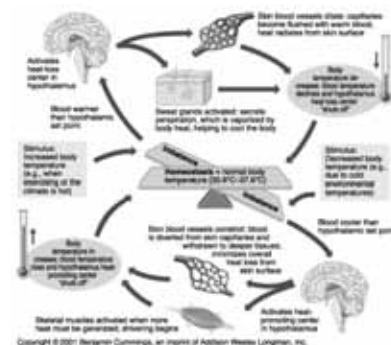


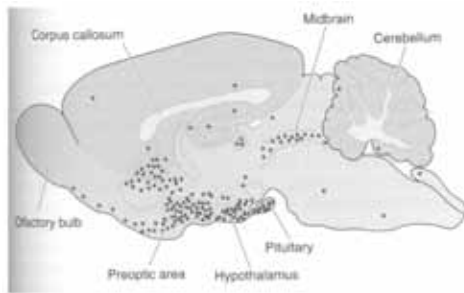
The 29th Annual Meeting of the Society for Medical Decision Making (October 20-24, 2007)

Mechanism of hot flashes

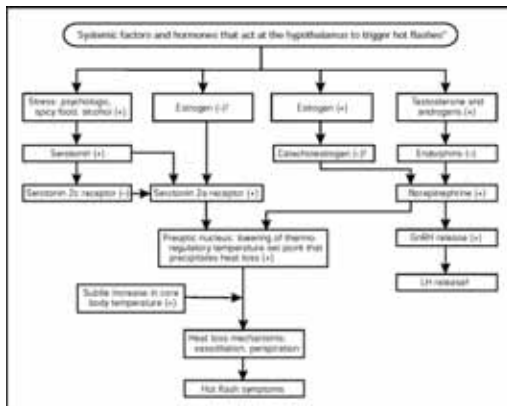
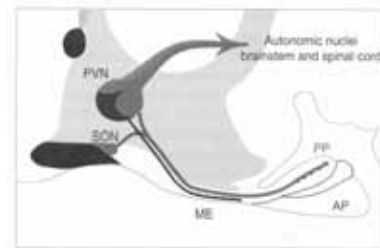
- Abnormality of thermoregulation
- Changes of neurotransmitters
- Peripheral vascular response

Thermoregulation

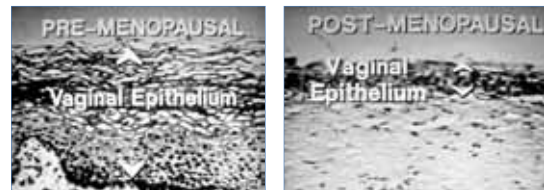




Functional associations of the paraventricular nucleus(PVN) and the endocrine and autonomic systems



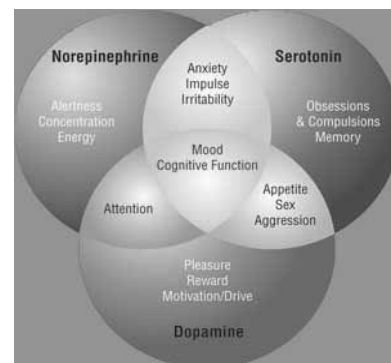
Atrophic Vaginitis



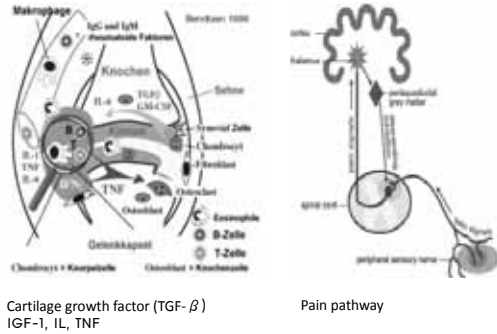
Psychological Symptoms

- Depressive mood
- Anxiety
- Sleep disturbance
- Memory impairment
- Temper
- Mood swing
- Lonely
- Headache

Psychological symptoms



Menopausal Arthralgia: Fact or fiction



Evaluation

여성갱년기 평가 검사

- 여성호르몬 검사: E2 \leq 20 pg/ml, FSH \geq 40 IU/L
- 고지혈증 검사, 심혈관계 예측지표 (hs-CRP)
- 심전도
- 체지방, 근육량 측정
- 골밀도 검사 (척추, 대퇴골: DEXA), 골 표지자 검사, 25(OH)D
- 척추 X-ray (단순촬영)
- 유방암 검사 (mammography), 유방 초음파 검사
- 복부 초음파 검사 (담석 확인)
- 기타 기본적인 혈액, 소변 검사 (간기능, 당뇨, 빈혈 등)
- 갑상선기능 검사
- 필요 시 자궁내막검사, 난소암 검사, 유즙분비호르몬 등

Menopause Rating Scale (MRS) 점수 = 0-44/ 0-4, 5-7, 8-15, \geq 16		없음 0	약간 1	보통 2	심함 3	매우 심함 4
1	안면홍조, 발한 (갑자기 가슴 두근거림, 맥박이 건너 뛴, 박동이 빨라짐, 가슴이 조여드는 느낌)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	심장불편감 (갑자기 가슴 두근거림, 맥박이 건너 뛴, 박동이 빨라짐, 가슴이 조여드는 느낌)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	수면문제 (잠들기 어려움, 수면을 지속하기 어려움, 잠에서 이르게 됨)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	우울한 기분 (기분이 저침, 슬픔, 쉽게 눈물이 남, 의욕 없음, 감정이 수시로 변함)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	과민성 (신경이 날카로워지는 느낌, 내성적 긴장감, 공격적으로 되는 느낌)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	불안감 (내적인 초조함, 공황상태가 되는 느낌)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	신체 및 정신적 피로 (일상생활 수행능력의 전반적인 감소, 기억력 감퇴, 집중력 감소, 건망증)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8	성적인 문제 (성적 욕구의 변화, 성행위의 변화, 성적 만족감의 변화)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	폐노문제 (에너지 부족, 소변이 자주 마려움, 요실금)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10	질 건조감 (질 부위의 건조감 또는 화끈한 느낌, 성교시 불편감)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11	관절 및 근육 불편감 (관절통증, 류마티스와 유사한 증상)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Treatment

호르몬 요법(Hormone Therapy)

- 생동일성 호르몬
 - 체내에서 분비되는 호르몬과 분자적, 화학적 구조가 동일
- 비생동일성 호르몬
 - 천연호르몬 (natural hormone)
 - 합성호르몬 (synthetic hormone)



Indication of HT

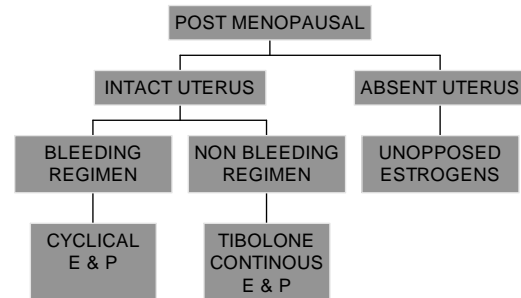
- Moderate Vasomotor Sx
- Vaginal atrophy -> topical estrogen
- Not used for Primary prevention cardiovascular ds
- Consider other drug for osteoporosis

**Lowest possible dose
shortest possible time**

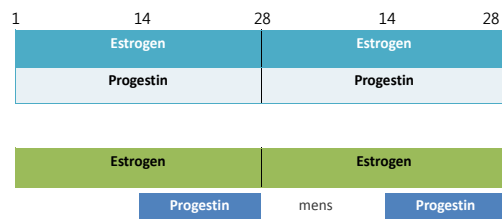
Clx of HT

- Pregnancy
- Abnormal vaginal bleeding
- Breast cancer
- Estrogen-dependent tumor
- Active DVT
- Pulmonary embolism
- Acute MI
- Cerebral infarction
- Liver disease
- Hypersensitivity to drug

Strategies of HRT



EPT: Continuous vs Cyclic



Ciane	estradiol hemihydrate 2 mg, norethisterone acetate 1 mg
Livial (리브론)	tibolone
Indivina	estradiol valerate 1/2 mg, medroxyprogesterone acetate 2.5/5 mg
Climen	estradiol valerate 2 mg, cyproterone acetate 1 mg
Divina	estradiol valerate 2 mg, medroxyprogesterone acetate 10 mg



Low Dose HT

- 저용량- 표준 용량의 ½
- 초저용량- 표준 용량의 ¼
- CEE 0.3mg/0.15mg
- 17β-Estradiol 0.5mg/0.25mg
- Transdermal estradiol 25mcg/14mcg



Cliovelle	estradiol hemihydrate 1.03 mg, norethisterone acetate 0.5 mg
Angeliq	estradiol hemihydrate 1.033 mg, drospirone 2 mg

- Prestwood study]
 - 0.25 mg 17β-estradiol w/ Cal 1300 mg + Vit D 1000 IU for 3 yr
 - BMD & Hot flushes effective, breast ca risk (-)



ET

Premina	conjugated equine estrogens 0.3/ 0.625 mg
Preda	estradiol hemihydrate 1.03 mg/ 2.07 mg
Prodynova	estradiol valerate 1 mg/ 2 mg
Climara patch	estradiol hemihydrate 3.9 mg/12.5 cm², weekly



- **Alternatives of HT**
 - progestin/ low dose oral contraceptives (IA)
 - nonhormonal prescription therapy (IB)
 - natural health products: limited evidence (IB)
- Vaginal bleeding after 12 months of amenorrhea should be investigated (IA).

Topical Apply & OC

Esgen vag cream	estropipate
Estreva gel	estradiol hemihydrate 1.0325 mg/g 0.5mg/puff x 3, daily
Estrodose gel	estradiol hemihydrate 0.62 mg/g
Yaz(yasmin)	ethinyl estradiol 0.02 mg, drospirone 3 mg
Triquilar	ethinyl estradiol 0.03 mg/0.04 mg/0.03 mg, levonorgestrel 0.05 mg/0.075 mg/0.125 mg
Evra patch	ethinyl estradiol 0.6 mg, norelgestromin 6 mg, weekly, for 3 wk

천연호르몬제제



- Phytoestrogen: 50mg/day
- Klimaktoplan: 1-2T po bid/tid
- Remifemin: 1T po bid
- Feramin-Q: 1-2T po bid



생동일성 호르몬



Bioidentical Hormone

- 콩(soy)이나 멕시코산 야생 Yam(Mexican yam) 등의 식물에서 추출
- 디오스게닌(diosgenin)이라는 화합물로부터 합성됨
- 스테로이드와 구조적으로 유사
- 프로게스테론으로 전환
- 안드로겐과 에스트로겐의 전구체 역할
- 체내 비결합 호르몬의 균형을 맞춤



Table 1. Synthetic and bioidentical estrogen preparations available in the United States^{2,22}

Estrogen	Brand
Bioidentical 17-beta estradiol (E2)	Alexis [®] , Climara [®] , Estraderm [®] , Fempatch [®] , Oestrone [®] , Viole [®] (all transdermal patches; Climax Patch [®] (E2 + norethindrone); Esting [®] , Femring [®] (vaginal rings); Estrace [®] , Estragel [®] (transdermal preparations); Vagifem [®] (vaginal tablets); Estace [®] (tablet and vaginal cream)
Ethinyl estradiol (EE)	Opren [®] (tablet and vaginal cream); Ortho-Est [®] (tablet)
Estriol (E3)	Not FDA approved
Non-bioidentical Estrogen estradiol	Brevicon [®] , Demulen [®] , Levlen [®] , Lo-Oval [®] , Lucrin [®] , Medicon [®] , Norello [®] , Norello [®] , Ortho-Cept [®] , Ortho-Cycle [®] , Ortho-Novum [®] , Ortho-Tri-Cycle [®] , Ovcon [®] , Tri-Levlen [®] , Tri-Norinyl [®] , Triphasil [®] , Nohva [®] (all tablets in combination with synthetic progestin); Estinyl [®] , Femminex [®] (tablet)
Esterified estrogens	Menest [®] (tablet)
Conjugated estrogens	Premarin [®] (tablet, vaginal cream); Prempro [®] , PremPhase [®] (tablet in combination with CEE)
Dienestrol	Ortho Dienestrol Cream [®] (vaginal cream)

Table 2. Synthetic and bioidentical progesterone preparations available in the United States^{2,23}

Progesterone	Brand
Bioidentical Progesterone (P4)	Cytone [®] , Uteron [®] (vaginal gel); Pro-Ges [®] (transdermal cream); Prometrium [®] (capsule)
Non-bioidentical Mifepristone/progesterone acetate (MPA)	Provera [®] , Anov [®] , Campho [®] , Cyclo [®] (tablet); PremPro [®] , PremPhase [®] (tablet in combination with CEE)
Norethindrone acetate	Acquin [®] , Micronor [®] , Nohvan [®] , Nor-QD [®] (tablet)
Norethindrone	Norlutal [®] (tablet)
Norgestrel	Oxone [®] (tablet)
Norgestrom	Ortho-Tri-Cycle [®] (tablet in combination with EE)
Levonorgestrel	Provera [®] (tablet in combination with EE)
Dienogest	Dienogest [®] (tablet)
Megestrol acetate	Megace [®] (tablet)

SSRI & 기타 제제



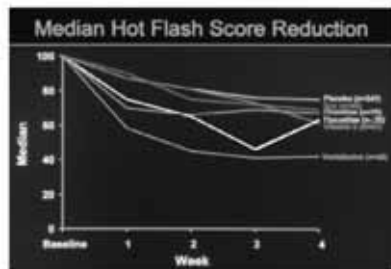
SSRI & SNRI

- 적응증]
 - 60대 이상의 여성에서 지속적이고 심한 홍조
 - 유방암의 병력
 - 열성 홍조와 심리적인 증상을 함께 호소
- 금기]
 - tamoxifen을 복용하고 있는 유방암 환자
 - ∴ 중간 활성물질인 endoxifen으로 전환되는 것을 방해

Table 3. Summary of effects on hot flush reduction.

	SSRI (effectiveness)	SNRI (effectiveness)
Better	Paroxetine (30~40%), Paroxetine CR (60~70%) (additional 13~41%)*	Venlafaxine (30~60%), (additional 33%)*
Good	Fluoxetine (20%), (additional 13%)* Citalopram (40~50%)	Desvenlafaxine (30~70%)
No effect	Sertaline (additional 3~18%)*	

CR: controlled release, *: additional effectiveness compared with those of control group.

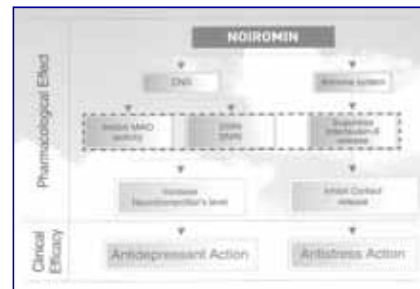


- Placebo
- Soy
- Clonidine
- Fluoxetine
- Vitamin E
- Venlafaxine

Figure. Hot flash score reduction (percentage of a baseline-week score) in the multiple North-Central treatment Group placebo-controlled double-blind clinical trials evaluating nonhormonal agents. The placebo arms from each of these trials are combined into one placebo curve.

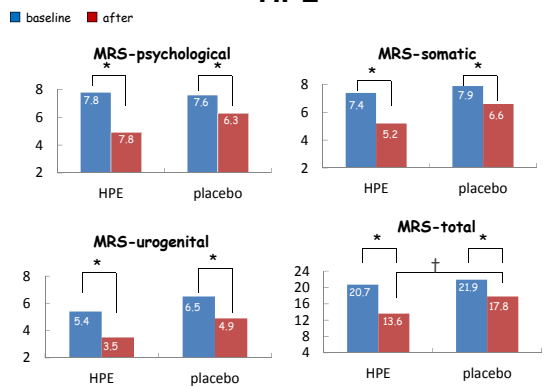
* Vit E (800IU) & behavioral interventions: 40-45%, no toxicity

NOIROMIN's Triple action



1. 신경 말단에서 Dopamine, Serotonin, Norepinephrine 재흡수 차단 → 농도증가
2. MAO 억제제로 Dopamine, Serotonin, Norepinephrine 등 신경전달물질의 대사 활성화
3. 면역조직계를 자극하여 Interleukin-6 방출 억제 → 스트레스 호르몬(cortisol) 분비 저하

HPE



*; P<0.05 by paired samples t-test

†; P<0.05 by ANCOVA (adjusting age and BMI)

Ginkgo Extract





- Lymphatic circulation: Entelon 150 mg bid
- Minerals
 - Mg: for metabolic SD
 - Zn: for hormonal secretion
- Gabapentin
- DHEAS



ANS disorder

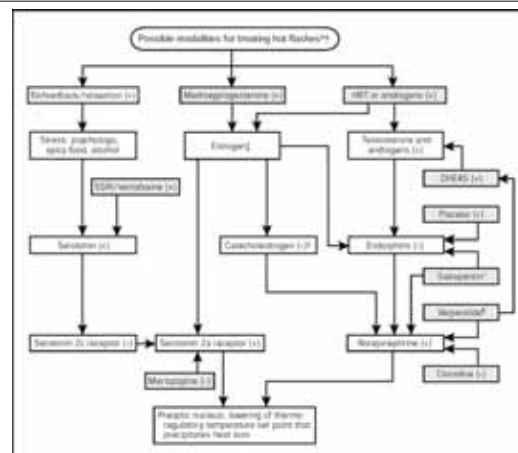
NAd

Ach

교감신경 흥분제	부교감신경 흥분제
Ephedrine Phenylephrine	사용하지 않음
교감신경 차단제	부교감신경 차단제
B-차단제 ex) Kerlone 0.5T QD	Atropine 진경제

- Anxiolytics
- Vitamines : VA, VB1/6/12, VC, VE
- Hormones

Summary



- HT remains the most effective treatment for menopausal symptoms but is only one option
→ combination therapy
- For most women under 60 the Risk/benefit ratio for HT is beneficial
- Vulnerable groups such as POF need particular attention
- Our role as experts is to provide upto date information, advice and guidance
- regular observation & f/up

