

NOVEL DELIVERY TECHNOLOGIES OF HRT

Review of the Advantages and Disadvantages

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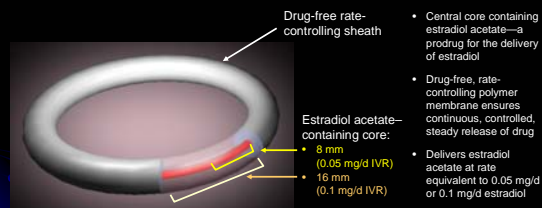
Why are we looking at new delivery systems?

- More constant serum levels (less fluctuations)
- Equal effectiveness
- Fewer adverse events
- Improved compliance and patient acceptance
- Improved safety profile
- Lowest effective dose
- Target local uterine effect with local progestogen

Novel Hormone Delivery systems

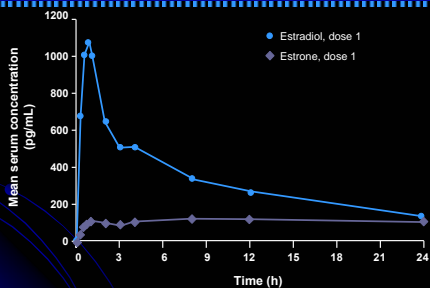
| | |
|--------------------------|----------------------------|
| Estradiol acetate ring | Estrogen-progestin ring |
| Nasal estradiol | Sublingual estradiol |
| Estradiol gel | Estradiol pellets |
| Ultralow-dose estradiol | 0.25 (oral), 0.014 (patch) |
| Progestogen IUDs | Progesterone vaginal gel |
| Transdermal Testosterone | |

Estradiol acetate ring delivery system



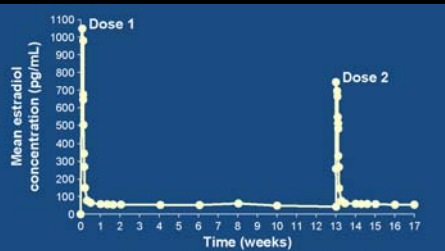
Al-Azawi F. et al. Poster presented at: British Menopause Society Congress, June 2001. Data on file, Warner Chilcott, Inc.

Mean serum estradiol and estrone profiles: Estradiol acetate ring 0.05 mg/d

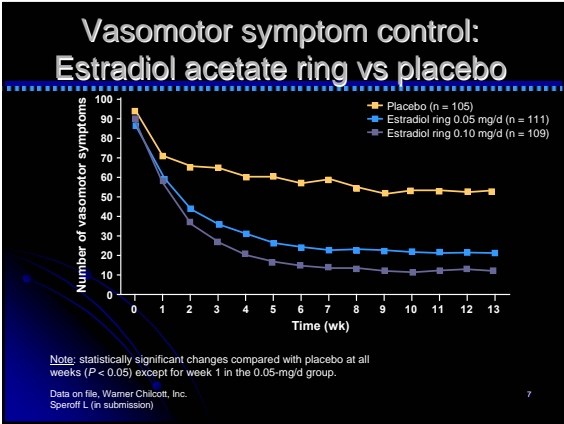


McNamee, de Vries. Poster presented at: North American Menopause Society, October 2001.

Mean serum estradiol profile: Estradiol ring 0.05 mg/d



Passmore et al. Poster presented at: British Menopause Society Congress, June 2001.



Estrogen ring: Patient complaints*

| | |
|--------------------------------------|----|
| Expulsion | 7 |
| Ring slippage | 5 |
| Discomfort and pressure | 5 |
| Discharge | 22 |
| Itch | 11 |
| Odor | 7 |
| Infection (vaginosis, yeast) | 5 |
| Tenderness / pain during intercourse | 2 |

*N = 70, 6-month trial.
Nash et al. *Am J Obstet Gynecol* 1999;181:1400-1406.

Sexual Activity*

| | Subjects (n) | % |
|---|--------------|------|
| Told partner of ring | 1180 | 71.1 |
| Partner felt ring | 473 | 28.5 |
| Partner had negative feelings | 134 | 8.1 |
| Ring interfered with sex | 119 | 7.2 |
| Patient had pain due to ring during sex | 113 | 6.8 |
| Partner had pain due to ring | 30 | 1.8 |

*Applies only to subjects who had sex while wearing the ring (n=1660).
Data on file, Warner Chilcott, Inc.

- ### Estradiol acetate ring: Advantages
- FDA approved for vasomotor, vulvar, and vaginal symptoms
 - Effective for 3 months
 - Available in two strengths (0.05 and 0.1 mg/d)
 - Easily inserted/removed
 - High level of acceptability
 - Low level of expulsion

- ### Estrogen ring disadvantages
- Not indicated for osteoporosis
 - Vaginal irritation
 - Discomfort
 - Need for progestin
 - Expulsion

- ### Nasal Estradiol
- Aqueous nasal formulation of estradiol
 - 300 mg/day (150 mg per nostril/day)
 - Mucociliary absorption
 - Pharmacokinetics
 - Rapid absorption- high brief plasma estradiol peak
 - Rapid fall to 10% within 2 hours
 - Untreated level by 12 hours
 - Brief stimulation of estradiol receptors
 - leads to gene activation
- Gompel et al. *Maturitas* 2000;38:209-215, Mattsson et al. *Am J Obstet Gynecol* 2000;182:545-552, Devissaguet et al. *Euro J Drug Metab Pharmacokin* 1999;24:265-271, Ozsoy et al. *J Gynecol Obstet* 2002;79:143-146, Mattsson. *Climacteric* 2002;2(Suppl 5):40-45, Palacios. *Climacteric* 2002;2(Suppl 5):52-59.

Nasal estradiol: Advantages

- Rapidly absorbed
 - Avoids first-pass metabolism
- Well tolerated
 - 15% discontinuation at 1 year
- Prevents bone loss
 - equivalent to 2 mg oral or .50ug patch
- Lower rates of withdrawal bleeding and mastalgia compared with oral therapy
 - 4.4% (n=134) withdrew AE: 2 mastalgia, 1 headache, 1 permanent runny nose, 1 allergy and 1 nasal prickling
- Lower rate of tumor induction (animal models)

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Nasal estradiol: Disadvantages

- Effectiveness in patients unknown with
 - nasal pathology
 - allergies
 - nasal and sinus infections
- Concern about effects of high bursts

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Sublingual micronized 17 beta-estradiol

- Pharmacokinetics
 - rapid, burst-like absorption
 - initial high estradiol levels fall rapidly during first 6 hours
- Results in significantly higher estradiol levels at 24 hrs
 - compared with 1 mg or 0.5 mg oral agents
- Favorable decreases in urine markers of bone metabolism
- Slight increases in spine and hip BMD at 1 year
- Cardiovascular benefits in ischemia and LV function

Price et al. *Obstet Gynecol* 1997;89:340-345.
Miller et al. *Menopause* 2000;7:319-326.

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Transdermal Overview Patches, gels, creams and rings

- Consistent delivery
- Lower doses lead to therapeutic hormone levels
- Avoids first-pass metabolism
- Absorption varies according to carrier vehicle, application location
- Rapid onset and rapid termination of action
- Continuation and compliance may be improved
- Dosages can be self-controlled (for some gels)¹
- Stable HDL and triglyceride levels

1. Vihitamaki et al. *Eur J Endocrinol* 2002;146:333-338.

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Medical indications for transdermal estradiol

- Smokers
- Alcoholics
- Liver disease, gallbladder disease
- Hyperinsulinemia
- Elevated triglyceride levels
- Poor control of symptoms
- Lactose intolerance

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17 B Estradiol gel

- Estradiol is suspended in a hydro-alcoholic gel
- Available in France for 20 years and Canada for 4
- In the US, will be available as pump-metered dose
 - 1.5 mg (equiv. of 0.5 mg oral estradiol)
 - 2.5 mg (equiv of 1.0 mg)
- Physiologic plasma concentrations of estradiol
- Steady state bioavailability is 82% compared with equivalent oral dose

www.healthanswers.com.au/drugdata
Moogari S et al. *J Clin Endo Metab*
1991;73:373-379

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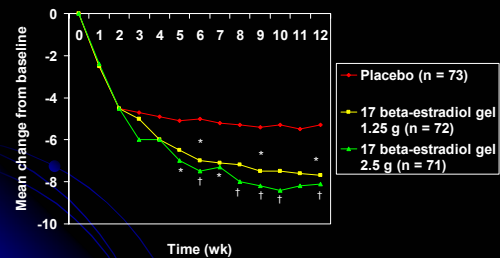
17 B Estradiol gel

- Skin acts as an intradermal reservoir and rate-controlling membrane
 - apply to a large surface area (wrist to shoulder) for maximal absorption
 - apply day 1-21/28-day cycle on both arms, abdomen, or inner thighs (similar rates of absorption)
 - Vehicle evaporates in 2 to 4 minutes leaving no residue (nonsticky, no odor)

www.rcanadapharmacy.com
www.healthcareers.com.au/drugdata

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Reduction of vasomotor symptoms with 17 beta-estradiol gel



*P < 0.05 vs placebo; †P < 0.001 vs placebo.
Adapted from data on file (Solvay).

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17 B Estradiol gel: Advantages

- Equivalent to oral and transdermal (patch) therapies in vasomotor relief
- Avoids first-pass hepatic metabolism
 - 1% increase triglycerides vs 34% with CEE
 - No increase in renin substrate or SHBG
- Increased BMD similar to CEE in lumbar spine (+5.6% vs +4.1%)
- Skin irritation considerably lower (1.1%)
- 97% rate gel as acceptable or convenient

Hirvonen et al. *Climacteric* 2000;3:262-270.
Nunez M. *Obstet Gynecol* 2000;95(4supp 1):S23 abstract
Moorjani S. et al. *JCEM* 1991;73:373-379

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Estradiol gels: Disadvantages

- Lacking long term safety data
- No fracture prevention data
- Need progestogen protection for uterus

Hirvonen et al. *Climacteric* 2000;3:262-270.
www.healthcareers.com.au/drugdata

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Declining dosages of estrogen

| | |
|--|--|
| Genant 1982 Lindsay 1984 | 0.625 mg conjugated equine estrogen appears ineffective (younger oophorectomized women) |
| Ettinger 1992, Evans 1996, Genant 1997, Recker 1999, Delmas 2001, Lindsay 2002 | 0.3 mg conjugated estrogen or equivalent preserves bone |
| Prestwood 2000, 2003 | 0.25 µg micronized 17 β-estradiol has effects on bone similar to 1.0 mg/d with a lower side effect profile |
| Ettinger (in submission) | 0.014 mg/d via transdermal patch benefits bone density in postmenopausal women |

Genant et al. *Ann Intern Med* 1982;97:699-705.
Lindsay et al. *Obstet Gynecol* 1984;63:759-763.
Ettinger et al. *Am J Obstet Gynecol* 1992;166:478-488.
Evans, Dawe. *Clin Endocrinol* 1996;44:793-94.
Genant et al. *Arch Intern Med* 1997;157:2609-2615.
Recker et al. *Ann Intern Med* 1999;130:897-904.
Delmas et al. *Am J Obstet Gynecol* 2001;184:32-40.
Lindsay et al. *JAMA* 2002;287:2666-2676.
Prestwood et al. *J Clin Endocrinol Metab* 2000;85:4462-4469.
Ettinger (in submission).

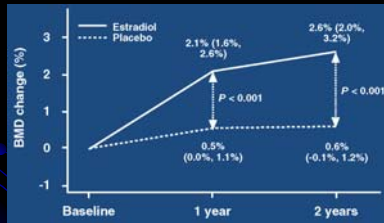
Ultralow-dose estradiol: Transdermal 0.014 estradiol patch

- Design
 - 2-year, double-blind, placebo-controlled, multicenter trial
 - 417 postmenopausal women 60 to 80 (mean, 67±5)
- Intervention
 - Placebo (n = 209)
 - 0.014 mg/d estradiol patch (n = 208)
 - 800 mg/d calcium, 400 IU vitamin D
- End points
 - Hip and spine bone mineral density at 2 years
 - Endometrial evaluation

Ettinger (in submission).

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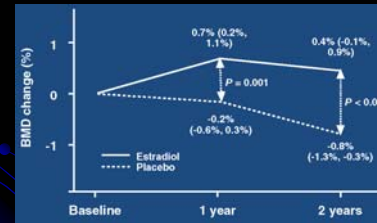
Ultralow-dose estradiol patch: Effects on lumbar spine BMD



Ettinger (in submission).

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Ultralow-dose estradiol patch: Effects on hip BMD



Ettinger (in submission).

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Ultralow-dose estradiol patch: Advantages

- Improves bone density in older women
- Does not increase rates of endometrial hyperplasia at 2 years
- Need exists for a revised definition of estradiol sufficiency in older women

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Ultralow dose therapies Disadvantages

- Not as effective in treating vasomotor symptoms or preventing bone loss
- Theoretically safer (no data)
- Lack of long term safety and efficacy
 - risk of breast cancer, endometrial cancer and fracture

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Nonoral progestogen delivery

- Estrogen and progestogen patches and rings
- Levonorgestrel IUD 20 µg, 10 µg
- Vaginal progesterone gel : 4%, 8%

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Levonorgestrel IUD compared with oral medroxyprogesterone acetate

| | Levonorgestrel | | Oral regimen |
|-------------------------------------|----------------|-----------|------------------------------------|
| | 10 µg IUD | 20 µg IUD | |
| Endometrial suppression after 12 mo | 97.9% | 100% | 38.1% |
| Endometrial hyperplasia after 12 mo | 0% | 0% | 0% |
| Bleeding after 6 mo | 95.6% | 98.2% | Typical cyclic withdrawal bleeding |

Raudaskoski et al. Br J Obstet Gynaecol 2002;109:136-144.

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10 µg vs 20 µg levonorgestrel IUD: Ease of insertion

- **10 µg**
 - Easy in 70%
 - Difficult in 4%
- **20 µg**
 - Easy in 46%
 - Difficult in 21%

Raudaskoski et al. *Br J Obstet Gynaecol* 2002;109:136-144.

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Progesterone IUD: Side effects

- **Rare**
 - Cervical perforation or laceration
 - Embedment of IUD
 - Device fragmentation
 - Neurovascular episodes (at time of insertion)
 - Pelvic inflammatory disease
- **Less rare**
 - Abdominal pain or cramping upon insertion
 - Continuing uterine bleeding on insertion
- **Post menopausal women-** difficulty with insertion

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Intrauterine devices: Advantages

- **Cost-effective**
- **Assured compliance**
- **Local effects instead of systemic reversible effects**
- **Long-term single-dose therapy (1 to ≥5 years)**

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Vaginal progesterone gel

- **Progesterone is absorbed orally**
 - >90% metabolized during first-pass effect
 - high levels of progesterone metabolites lead to increased drowsiness and dizziness
- **Not well absorbed through skin**
- **Progesterone vaginal (polycarbophil) gel**
 - controlled and sustained release properties
 - local direct vaginal uptake
 - Results in preferential uterine uptake
 - plasma levels remain physiologic
 - endometrial changes produced

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Progesterone vaginal gel—4%, 8%

- **Multicenter, randomized, parallel, open-label 3-month trial**
 - 127 women with secondary amenorrhea; qod x 6 doses
- **Progestational changes on endometrial biopsy**
 - 4% gel: 92%
 - 8% gel: 100%
- **Compliance >98%**
- **Most side effects decreased**

Warren et al. *Am J Obstet Gynecol* 1999;180:42-48.

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Transdermal estradiol and vaginal progesterone gel: 1-year trial

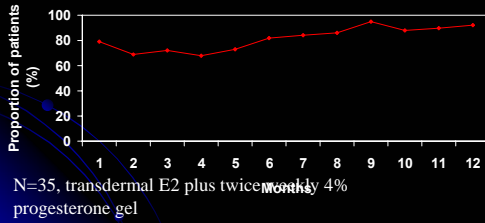
- **Prospective observational trial**
 - 26/ 35 (74.3%) women completed
- **Blood pressure and weight dropped significantly at month 3 and remained lower**
- **100% amenorrheic at 1 year**
- **Endometrial thickness significantly greater than baseline at 1 year**
 - Baseline 3.6 mm (+/-0.9), endometrial atrophy in all
 - 12 months, 4.6 mm (+/- 0.9mm),
 - endometrial atrophy 92.3%

Cicinelli et al. *Am J Obstet Gynecol* 2002;187:556-560.

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Amenorrhea rates with progesterone gel 4%

Amenorrhea rates for patients completing study per protocol



N=35, transdermal E2 plus twice weekly 4% progesterone gel

Cicinelli et al. Am J Obstet Gynecol. 2002;187:556-560.

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Estrogen plus vaginal progesterone gel: cyclic vs continuous

Continuous estrogen

- + cyclic progesterone vaginal gel 4% days 1-10 (69 women)
- + continuous progesterone vaginal gel 4% twice weekly (67 women)

At 6 months

- Cyclic therapy**
 - 63 (91.9%) predictable withdrawal bleeding
- Continuous therapy**
 - 54 (80.6%) amenorrheic

de Ziegler et al. Hum Reprod 2000;15:149-156.

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Progesterone gel Advantages and Disadvantages

Advantages

- plasma levels remain physiologic
- local direct vaginal uptake
 - results in preferential uterine uptake
- Fewer side effects
- Theoretically less systemic effects

Disadvantages

- Lack of long term efficacy and safety data with regards to protection against endometrial cancer

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Transdermal Testosterone Treatment in Women with Impaired Sexual Function After Oophorectomy

Design

- Multi-center, double-blind, randomized, placebo-controlled, crossover study
- Three treatment periods

| Screen/Baseline | Period I | Period II | Period III |
|-----------------|----------|-----------|------------|
| 4wk | 12 wk | 12 wk | 12 wk |

Treatment Regimens

All patients maintained on oral CEE (≥ 0.625 mg) during study, with twice weekly application of placebo or testosterone patches

CEE + 0 μ g/day testosterone (2 placebo patches)

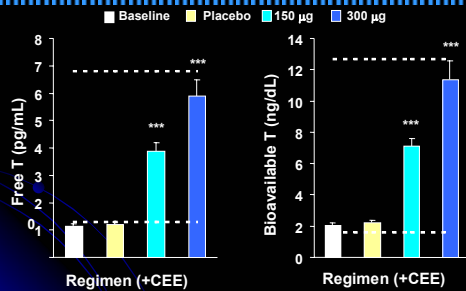
CEE + 150 μ g/day testosterone (1 testosterone/1 placebo patch)

CEE + 300 μ g/day testosterone (2 testosterone patches)

Shiffren J. NEJM 2000; 343, p.682-688.

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Free T Increased into Normal Range; Bioavailable T Increased within Normal Range



*** Endocrine Sciences normal range for cycling women

***P<0.001 for comparison with placebo

Treatment of surgically menopausal women with transdermal testosterone:

- Significantly increased frequency of sexual activity, pleasure/orgasm (BISF-W), and psychological well-being (PGWB) at higher testosterone dose
- Well tolerated locally and systemically
 - no clinically significant effects on hirsutism, acne, cholesterol, glucose or insulin levels
- Increased free and bioavailable testosterone in dose-dependent manner within physiologic range
- Did not alter estrogen concentrations

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Bioidentical/compounded hormones

- **Advantages**
 - 'natural'
 - 'milder'
 - 'safer'
- **Disadvantages**
 - Lack safety/efficacy data
 - Lack long term data
 - Concern about batch to batch variability or contamination
 - Not FDA approved, not regulated

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Novel delivery technologies of HRT

- **Estradiol vaginal ring**
 - - sustained levels for 3 months
- **Nasal/sublingual estradiol**
 - - high brief estradiol peak
- **17 B estradiol gel-**
 - Skin acts as intradermal reservoir + rate-controlling membrane
- **Ultra low estradiol- patch (0.014)-**
 - maintain BMD without uterine stimulation at 2 years
- **Progestogen IUDs**
 - - sustained local uterine effect
- **Progesterone vaginal gel**
 - More local effect, fewer side effects

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Novel Technologies of HRT

- **Effective at reducing vasomotor symptoms**
- **Maintain BMD**
- **Potential for fewer side effects**
 - -less fluctuations in levels
- **Increased compliance and patient acceptance**
- **Avoid first-pass hepatic effects**

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Conclusion: novel technologies

- **How important is the route of administration?**
 - Do they meet the goal of sustained levels with little fluctuation?
 - Advantage to bypassing first-pass hepatic effect?
- **What is the lowest effective dose of estrogen?**
- **Is the lowest dose dependent on**
 - delivery system?
 - women's age?
 - her baseline estradiol?
- **Is different safer or better?**

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Dr. JoAnn Pinkerton – Questions & Answers

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