

The Clinical Significance of $\Delta^{8,9}$ -Dehydroestrone Sulfate in Treating Menopausal Vasomotor Symptoms

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DISCLOSURES

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INTRODUCTION

The US Food and Drug Administration and several women's health organizations recommend that hormone therapy (HT), the standard for treating menopausal vasomotor symptoms, be used at the lowest effective dose and for the shortest duration appropriate for each individual consistent with therapeutic goals.^{1,4}

Levels of endogenous hormones typically decline over 3 to 4 years during the menopausal transition, resulting in symptoms that are frequent or severe enough to affect a woman's quality of life or capacity to function. Many women request symptom relief from a clinician during this period. The importance of low-dose therapy and the need to individualize treatment type and duration of HT have become central concepts in managing the care of menopausal women (**SEE SIDEBAR, *Hormone therapy: prevalence, type, and duration***).

For women who have a uterus, this standard is applied to estrogen plus progestin therapy (EPT), the recommended treatment for moderate-to-severe vasomotor symptoms associated with menopause. The addition of progestin is understood to lower the risk of endometrial cancer in this population. For women who have undergone hysterectomy, or who have a uterus but who are using progesterone intermittently, the lowest effective dose of estrogen alone is the preferred option.²

TABLE 1

Selected oral and transdermal estrogen products

Brand Name	Generic	Route	Available strengths
Cenestin®	Synthetic conjugated estrogens, A	Oral	0.3 mg 0.45 mg 0.625 mg 0.9 mg 1.25 mg
ENJUVIA™	Synthetic conjugated estrogens, B	Oral	0.3 mg 0.45 mg 0.625 mg 1.25 mg
Estrace®	Estradiol tablets, USP	Oral	0.5 mg 1.0 mg 2.0 mg
	Estradiol vaginal cream, USP, 0.01%	Vaginal cream	0.01%
Menest®	Esterified estrogen tablets, USP	Oral	0.3 mg 0.625 mg 1.25 mg 2.5 mg
Ogen®	Estropipate	Oral	0.625 mg 1.25 mg 2.5 mg
	Estropipate vaginal cream, USP	Vaginal cream	1.5 mg/g
Premarin®	Conjugated equine estrogens tablets, USP	Oral	0.3 mg 0.45 mg 0.625 mg 0.9 mg 1.25 mg
	Conjugated equine estrogens vaginal cream in a nonliquifying base	Vaginal cream	0.625 mg/g
Alora®	Estradiol transdermal system	Transdermal patch	0.025 mg 0.05 mg 0.075 mg 0.1 mg
Climara®	Estradiol transdermal system	Transdermal patch	0.025 mg 0.0375 mg 0.05 mg 0.06 mg 0.075 mg 0.1 mg
Estraderm®	Estradiol transdermal system	Transdermal patch	0.05 mg 0.1 mg
FemPatch®	Estradiol transdermal system	Transdermal patch	0.05 mg 0.1 mg
Vivelle-Dot®	Estradiol transdermal system	Transdermal patch	0.037 mg 0.05 mg 0.075 mg 0.1 mg
EstroGel®	Estradiol gel	Transdermal gel	0.06% gel
Estrasorb®	Estradiol topical emulsion	Lotion	0.05 mg

HORMONE THERAPY: PREVALENCE, TYPE, AND DURATION

The majority of women on hormone therapy (HT) take estrogen only, as documented in an analysis of data from a large national sample drawn from the 1999 National Health Interview Study (NHIS).¹ While statistics for HT use may have shifted after discontinuation of the Women's Health Initiative, the analysis remains valuable for highlighting trends of estrogen-only and estrogen/progestin therapy within this patient population.

In the NHIS, approximately 24% of women over age 40 were HT users. Of these, 30% took combination estrogen/progestin, while 70% were on estrogen-only therapy. This figure was closely associated with age and hysterectomy status. Current use of estrogen/progestin or estrogen-only therapies among women older than 40 years who

had undergone hysterectomy was 2.7% and 44.8%, respectively. For women age 40 and older who had not undergone hysterectomy, current use was 9.2% and 5.3%, respectively.

Duration of use varied with the type of therapy and hysterectomy status. Of all women 40 years of age and older, only 3% had used estrogen/progestin for at least the past 5 years, while 10% had used estrogen only for the same 5-year period. The highest percentage and duration was among women with a history of hysterectomy, who were on estrogen-only therapy.

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Methods of administering estrogen at low doses in accordance with the recommended criteria include an assortment of therapies that vary by pharmacokinetics and route of administration, and can be tailored to the needs of the patient⁵ (**SEE SIDEBAR, *Individualizing hormone therapy***). Within this category are estradiol preparations (micronized estradiol, esterified estrogens, and piperazine estrone sulfate) and conjugated estrogens. Although most therapies consist of oral HT, some patients prefer nonoral HT systems that deliver estradiol transdermally. Currently, preparations of estrogen alone and estrogen plus progestin are available in a variety of dosages, in strengths that range from 0.3 to 2.5 mg. Delivery systems include oral tablets, creams, lotions, injections, vaginal rings and tablets, and transdermal systems. Choices for oral and transdermal estrogen therapy are shown in **TABLE 1**.

The effort to maximize the clinical benefits of HT at low doses has not been confined to alterations of dose or method of administration. Attention has focused on an examination of the

potency and distinct characteristics of various components in conjugated and esterified estrogens. Delta^{8,9}-dehydroestrone sulfate has emerged as a compound of special interest because of its unique tissue receptor binding versus tissue activity characteristics both in vitro and in vivo.⁶ The compound is believed to play an important role in the wide range of therapeutic benefits observed with conjugated equine estrogens (CEE).⁷

Methods of administering estrogen at low doses include an assortment of therapies that vary by pharmacokinetics and route of administration.

Recently, a roundtable symposium of leading physicians in women's health gathered to discuss the unique pharmacologic and clinical effects of Δ^{8,9}-dehydroestrone sulfate. They reviewed data that suggested a role for Δ^{8,9}-dehydroestrone sulfate in helping achieve clinical efficacy at low doses. The discussion focused on the presence of this active

INDIVIDUALIZING HORMONE THERAPY

If treatment is to be tailored to the individual, it is important to discuss risks, benefits, preferences, and treatment goals to determine the most efficacious therapeutic regimen.

No single preparation is suitable for all women. Clinicians should discuss the different methods of administration in terms of convenience and with regard to the patient's other medical conditions.

For all patients, therapy should begin with the lowest effective dose. The patient should be seen again in 4 to 6 weeks and, if symptoms persist, the dose can be raised until symptoms abate. Patient comfort and confidence in the

therapy are important components to help ensure compliance.

Important Considerations in Individualizing Therapy^{1,2}

- Set clear goals and expectations
 - Helps patients assess progress and fosters communication if adjustments are needed
- Prescribe the lowest effective dose
- Re-evaluate periodically
- Adjust therapy to the patient's clinical response and needs
 - Therapy can be titrated as necessary

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ingredient in Premarin® (CEE) and ENJUVIA™ (synthetic conjugated estrogens, B [SCE-B]).⁸

BACKGROUND

Delta^{8,9}-dehydroestrone sulfate was first identified in 1975 during evaluations of the constituent estrogens in CEE.⁷ Data were presented that demonstrated $\Delta^{8,9}$ -dehydroestrone sulfate possessed unique pharmacologic properties.⁷

Delta^{8,9}-dehydroestrone sulfate has emerged as a compound of special interest because of its unique tissue receptor binding characteristics.

Estrogen activity

There are at least 2 distinct estrogen receptors (ERs), ER- α and ER- β , found throughout body

tissues in different patterns of distribution. When an estrogen binds to an ER, the result is activation of the receptor. The receptor complex binds to DNA and stimulates gene transcription. The biologic effect of this activity is determined, in part, by the expression of ER- α and ER- β in that tissue. This helps account for the tissue selectivity observed with different estrogens.⁹

It is also understood that the biologic activity of an estrogen is not necessarily proportional to its binding affinity for ERs. For example, although $\Delta^{8,9}$ -dehydroestrone sulfate has only 1% of the binding affinity of estradiol, it exhibits high estrogenic activity in proportion to its binding affinity (TABLE 2).

A unique pharmacokinetic profile

In the 2 conjugated estrogens products containing $\Delta^{8,9}$ -dehydroestrone sulfate, SCE-B and CEE, this compound represents less than 5% of the estrogenic compounds present. After oral dosing of

CEE the plasma concentration of the metabolite of $\Delta^{8,9}$ -dehydroestrone reaches approximately 34% of the combined concentrations of the metabolites of estrone and equilin.⁷ The pharmacokinetic parameters of $\Delta^{8,9}$ -dehydroestrone, estrone, and equilin are shown for SCE-B in **TABLE 3**.⁸

These parameters were studied under fasting conditions. In this single-dose study, the peak plasma concentration of $\Delta^{8,9}$ -dehydroestrone was reached 8 hours after the administration of two 0.625-mg tablets and had a half-life of just over 14 hours. These values suggest that SCE-B can be expected to reach steady-state plasma levels within several days of starting treatment. At that time, levels should be steady throughout the full 24 hours.

Contributing to steady estrogen plasma levels is the delivery system of SCE-B, which combines a Surelease® (aqueous ethylcellulose dispersion) technology coating with a cellulose-based polymer tablet design. The resulting slow release of estrogens into the gastrointestinal tract, delivering steady plasma levels throughout the day and night, may help diminish issues associated with dissolution failures reported with other conjugated estrogen therapies (ET).¹⁰

Selective, potent activity both in vitro and in vivo

Pharmacology studies indicate that $\Delta^{8,9}$ -dehydroestrone is a centrally active and selective agent with high potency at ERs (**FIGURE**).^{11,12} In studies using animal luteinizing hormone-releasing hormone (LHRH) neuronal cells, both $\Delta^{8,9}$ -dehydroestrone and its metabolite, 17β - $\Delta^{8,9}$ -dehydroestradiol, activated endogenous ERs in vitro with a high degree of potency.¹¹ By activating these receptors in vivo, $\Delta^{8,9}$ -dehydroestrone can modulate gene expression in LHRH neuronal cells, suggesting that this compound can influence luteinizing hormone (LH) release from the central nervous system.¹²

TABLE 2

Estrogen receptor binding affinity and biologic activity

Rank	Human ER binding	Biologic potency*
1	17β -Estradiol	17β -Estradiol
2	17β -Dihydroequilin	$\Delta^{8,9}$ -Dehydroestrone
3	17β -Dihydroequilenin	Estrone
4	17α -Dihydroequilin	17β -Dihydroequilenin
5	17α -Estradiol	Equilenin
6	Estrone	17β -Dihydroequilin
7	Equilin	Equilin
8	17α -Dihydroequilenin	17α -Dihydroequilin
9	$\Delta^{8,9}$ -Dehydroestrone	17α -Dihydroequilenin
10	Equilenin	17α -Estradiol

*Biologic potency is measured by the activation of the gene C-3. Adapted from Dey M, et al. *Maturitas*. 2000;34(suppl 2):S25-S33.

What do the clinical data show on $\Delta^{8,9}$ -dehydroestrone sulfate?

A pilot study of the clinical effects of $\Delta^{8,9}$ -dehydroestrone sulfate by Baracat et al confirmed this estrogen's selective and potent activity.⁶ Thirty menopausal women were randomly assigned to 1 of 3 treatment groups for 12 weeks: $\Delta^{8,9}$ -dehydroestrone sulfate (0.125 mg/d; n = 10), estrone sulfate at a 10-times higher dose (1.25 mg/d; n = 10), or estrone sulfate plus $\Delta^{8,9}$ -dehydroestrone sulfate at these doses combined (n = 10). Patients were instructed to record the number and severity of vasomotor symptoms on daily diary cards. Data regarding bone loss, neuroendocrine activity, and lipids were also collected.

Vasomotor symptoms—Primary results demonstrated a significant suppression of hot flashes in the $\Delta^{8,9}$ -dehydroestrone sulfate group, reaching more than 95% suppression in all parameters of vasomotor symptoms. This was equal to the effect observed with a 10-fold higher dose of estrone sulfate (1.25 mg/d versus 0.125 mg/d for $\Delta^{8,9}$ -dehydroestrone sulfate), confirming the higher

TABLE 3

Mean pharmacokinetic characteristics of conjugated estrone, equilin, and $\Delta^{8,9}$ -dehydroestrone

	C_{max} (ng/mL)	t_{max} (h)	t_{1/2} (h)	AUC_{0-48h} (ng*h/mL)
Baseline-adjusted estrone (total) (% CV)	3.74 (29)	8.00 (27)	14.26 (26)	62.03 (34)
Equilin (total) (% CV)	3.69 (44)	8.05 (36)	11.28 (28)	58.25 (53)
$\Delta^{8,9}$ -dehydroestrone (total) (% CV)	0.74 (32)	7.55 (37)	14.14 (26)	12.93 (39)

* $\Delta^{8,9}$ -dehydroestrone is less than 5% of estrogenic content.

C_{max} = peak plasma concentration; t_{max} = time peak concentration occurs; t_{1/2} = apparent terminal-phase disposition half-life;

AUC = total area under the concentration-time curve from time 0 to time of last quantifiable concentration (48 h); CV = coefficient of variance.

Source: ENJUVIA™ [package insert]. Pomona, NY: Duramed Pharmaceuticals; 2004.

biologic potency of $\Delta^{8,9}$ -dehydroestrone sulfate on vasomotor symptoms.

A pilot study of the clinical effects of $\Delta^{8,9}$ -dehydroestrone by Baracat et al confirmed the selective and potent activity of this estrogen.

Results were similar in a subgroup analysis among 15 highly symptomatic women, patients who had at least 7 hot flashes per day at baseline (TABLE 4). Five patients in each group met this standard. The average number of daily hot flashes at baseline were 10.6, 9.4, and 8.7 for the estrone sulfate, $\Delta^{8,9}$ -dehydroestrone sulfate, and combination groups, respectively. Patients taking $\Delta^{8,9}$ -dehydroestrone sulfate alone (n = 5) achieved a 95% decrease in the number of hot flashes after 8 weeks of treatment, whereas women taking estrone sulfate (n = 5) at the much higher dose achieved an 89% reduction. The combination of the 2 compounds resulted in 100% suppression of hot flashes for these highly symptomatic women. Pairwise comparisons demonstrated statistically significant differences between the estrone sulfate group and the $\Delta^{8,9}$ -dehydroestrone sulfate groups (P = .03) and between the estrone sulfate and the combination groups (P = .02) at 84 days.

Bone resorption—In the same study, $\Delta^{8,9}$ -dehydroestrone sulfate also had a significant effect on a marker of bone resorption (urinary N-telopeptide). Excretion levels were reduced by approximately 40% in the $\Delta^{8,9}$ -dehydroestrone sulfate group. This reduction was similar to that of estrone sulfate at the much higher dose, which suggests effective protection against bone loss associated with estrogen depletion.

Neuroendocrine parameters—The neuroendocrine effects observed with $\Delta^{8,9}$ -dehydroestrone sulfate in this clinical study were consistent with data gathered in preclinical studies. Delta^{8,9}-dehydroestrone sulfate significantly reduced the serum levels of follicle-stimulating hormone at 14 days, as did treatment with estrone sulfate or the 2 in combination. A significant 30% reduction of LH was induced by $\Delta^{8,9}$ -dehydroestrone sulfate after 56 days of treatment. Reductions were also significant in both of the other groups, although reductions were not significant at day 84 for estrone sulfate or the combination. Prolactin levels remained stable in all groups.

Lipids—Delta^{8,9}-dehydroestrone sulfate did not significantly affect high-density lipoproteins (HDL) or low-density lipoproteins (LDL) and had only a marginal effect on serum globulins, which suggests little, if any, effect on the liver. No elevations in triglyceride levels were observed for any of the

TABLE 4
Percent change from baseline in number of hot flashes

Time period	Estrone sulfate 1.25 mg (n = 5)	$\Delta^{8,9}$ -dehydroestrone sulfate 0.125 mg (n = 5)	Estrone sulfate + $\Delta^{8,9}$ dehydroestrone sulfate (n = 5)
8 wk	88.06 ± 3.77	95.00 ± 3.33	100.00 ± 0.00
12 wk	89.17 ± 6.12	98.33 ± 1.67	100.00 ± 0.00

Adapted from Baracat E, et al. *J Clin Endocrinol Metab.* 1999;84:2020–2027.

groups. Estrone sulfate produced the changes in lipids typically expected with estrogen therapy—a decrease in LDL and an increase in HDL.

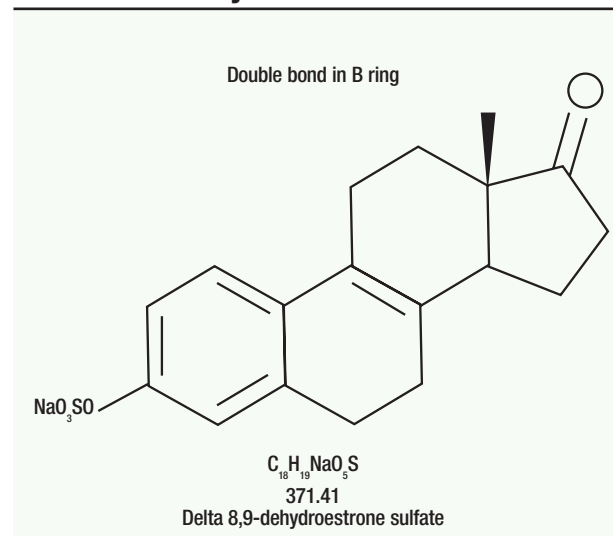
Safety—Assessments revealed no clinically significant changes in overall health.

It is important to recognize the limitations of this study. The patient groups were small, and the amount of $\Delta^{8,9}$ -dehydroestrone sulfate taken by patients (0.125 mg) was far greater than that found in either CEE or SCE-B. Nonetheless, data suggest that $\Delta^{8,9}$ -dehydroestrone sulfate is a potent, clinically active conjugated estrogen that targets specific tissues and receptors, with the potential to effectively achieve several desired effects of HT without or while minimizing unwanted effects, such as breast tenderness.

Discussion

As an active ingredient that can provide potent estrogenic activity for the effective relief of vasomotor symptoms while having antagonistic activity or no effect on peripheral tissue sites, $\Delta^{8,9}$ -dehydroestrone sulfate holds great promise for the optimization of ET. Of particular interest are compounds that can achieve a reduction of troublesome vasomotor symptoms and help reduce bone loss while minimizing the effects on other peripheral tissues normally affected by nonselective estrogens.

The high potency of $\Delta^{8,9}$ -dehydroestrone sulfate may be key to the efficacy of low-dose therapy with SCE-B. In a placebo-controlled trial among 281 highly symptomatic menopausal women, patients taking 0.3 mg SCE-B, (n = 66) experienced significant reductions in the frequency of vasomotor symptoms by week 3 and in the

FIGURE
Chemical structure of $\Delta^{8,9}$ -dehydroestrone sulfate


The unique chemical structure of $\Delta^{8,9}$ -dehydroestrone sulfate consists of a conjugated double bond in the B ring.
Chemical structure of $\Delta^{8,9}$ -dehydroestrone sulfate.
The unique chemical structure of $\Delta^{8,9}$ -dehydroestrone sulfate consists of a conjugated double bond in the B ring.

SOURCE: ENJUVIA™ [package insert]. Pomona, NY: Duramed Pharmaceuticals; 2004.

severity of their symptoms by week 4.¹³ Treatment was well tolerated. No differences were observed in the incidence of treatment-related adverse events between the placebo and active treatment group. None of the patients in this group reported breast pain.¹³

Conclusion

While many practitioners may not be familiar with the properties of $\Delta^{8,9}$ -dehydroestrone sulfate, the need for effective low-dose ET will potentially lead

more clinicians to learn about specific components of ET that show tissue selectivity and high potency. Participants at the roundtable expressed interest in seeing further study into $\Delta^{8,9}$ -dehydroestrone sulfate and similarly selective compounds.

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