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WHITE PAPERS

Transdermal (TD) Estradiol (E2)

A Critical Review of the Literature and Available Data

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INTRODUCTION

This material is educational and not an endorsement for a particular HRT dose or route of administration. The tables and charts on **pages 2 and 3** summarize the available data to help us navigate this topic. This document will explore all relevant data in detail.

TREATMENT/DOSING

- The scientific literature suggests doses as low as 0.014-0.025mg for E2 patches and 0.25mg for E2 gel products can be clinically impactful, though doses are highly product specific for E2 gels. Higher doses increase the clinical impact at the expense of higher E2 exposure.
- Low dose patches contain 0.4-5.0mg of E2 and deliver 0.025mg of E2 daily. This dose increases bone mineral density (BMD) and improves vasomotor symptoms (VMS), vulvovaginal (VVA) symptoms, and other related symptoms.
- Low dose offerings of FDA-approved E2 gels contain 0.25-1.5mg of E2 daily. These doses are also effective but do show some delay in improving BMD and VMS compared to low dose E2 patches, implying the doses are effectively "low."
- Higher doses of FDA-approved gels are more effective at improving BMD and VMS symptoms showing no delay, at the expense of higer total estrogen exposure.

LABORATORY MONITORING

- Serum or urine levels just outside the postmenopausal range and into the lower part of the premenopausal (luteal) range may be optimal targets for both E2 patches and gels. Serum, 20-60pg/mL; DUTCH, 0.7-1.8ng/mg.
- **SERUM** levels correlate to clinical improvements for both E2 patches and gels as it relates to VMS, BMD, VVA, and changes in FSH, lipids, SHBG, and the endometrium.
- **URINE** levels generally parallel serum levels and clinical outcomes with TD E2 gels (DUTCH data) and patches (DUTCH and published data), although no studies have tied clinical outcomes directly to urine levels. The DUTCH Test also includes estrogen metabolites.
- **SALIVA** testing should not be used with creams or gels as its exaggerated values do not appear to correlate to any studied clinical outcomes.
- **DUTCH** may be optimal with E2 creams and gels given the rapid up-and-down serum pattern.

TABLE 1: FDA APPROVED E2 GELS							
BRAND	DOSE	DAILY E2 (MG)	SERUM (PG/ML)	VMS	BMD	VVA	REFERENCES
Estrogel	Ultra-Low	0.27	11.7	Delayed	*	Failed	1
Divigel	Low	0.25	16	Delayed	*	Success	2,3
Elestrin	Low	0.52	9	Delayed	*	Success	4,5
Evamist	Low	1.53	19-23	Delayed	*	*	6,7
Estrasorb	Low	2.9	30	Success	*	*	8,9
Estrogel	Low	0.375	21	Success	*	Success	1
Estrogel	Moderate	0.75	33.5	Success	Delayed	Success	1,10,11,12,13
Divigel	Moderate	0.50	31	Success	*	Success	2,3
Elestrin	Moderate	1.04	32	Success	*	Success	4,5
Evamist	Moderate	3.06	24-32	Success	*	*	6,7
Estrasorb	Moderate	5.7	43	Success	*	*	8,9
Estrogel	High	1.5	65	Success	Success	Success	1,10,11,12,13
Divigel	High	1.0	62	Success	*	Success	2,3
Elestrin	High	1.56	60	Success	*	*	4,5
Evamist	High	4.59	31-40	Success	*	*	6,7
Estrasorb	High	8.6	63	Success	*	*	14
Estrogel	High+	3.0	102.9	Success	Success	*	12,15

"Low" = lowest recommended or studied dose. All products listed above are considered E2 gels except Estrasorb, which is an emulsified product

TABLE 2: FDA APPROVED E2 PATCHES							
BRAND	DOSE E2 (MG)	DAILY E2 (MG)	SERUM (PG/ML)	VMS	BMD	VVA	REFERENCES
Menostar	1	0.014	8.6, 13.7	Success	Success	Success	16, 17, 18
Alora	0.77	0.025	24.5	*	Success	*	19
Climara	2	0.025	22	Success	Success	*	20
Vivelle-Dot	0.39	0.025	*	*	Success	*	21
Vivelle-Dot	0.585	0.0375	34	Success	Success	*	21
Esclim	5	0.025	15.5	Success	*	*	22
Estraderm	*	0.025	*	*	Success	*	23
Alora	1.5	0.05	64	Success	Success	Success	19
Menorest	4.4	0.05	48.5	*	*	*	24
Climara	3.8	0.05	41	Success	Success	*	20, 24
Vivelle-Dot	0.78	0.05	57	Success	Success	*	21
Esclim	10	0.05	26.3	Success	*	*	22
Estraderm	4	0.05	32	Success	*	*	23
Alora	3.1	0.1	98	Success	Success	Success	19
Climara	7.6	0.1	87	Success	Success	*	20
Vivelle-Dot	1.56	0.1	89	Success	Success	*	21
Esclim	20	0.1	51.4	Success	*	*	22
Estraderm	8	0.1	74	Success	*	*	23

"Low" = lowest recommended or studied dose. All products listed above are considered E2 gels except Estrasorb, which is an emulsified product

EXECUTIVE SUMMARY

QUESTION

Saliva results suggests common E2 gel and cream doses are delivering much more hormone than even the highest E2 patch dose. Does any clinical data confirm this observation?

ANSWER

Published research demonstrates, and this document will describe in detail, that the clinical data more closely aligns with serum (for E2 gels) and urine (for E2 gels and creams) and contradicts exaggerated salivary levels.

What About Compounded E2 Creams?

- *There are presently no studies clinically validating compounded E2 creams, although they may be effective.*
- *Only one published study was found reporting serum results when using compounded E2 creams. Available data suggests that results may move up-and-down quickly (see graph on* **page 11***), making urine a better testing option. [See reference:* **27***]*
- *DUTCH results have been shown to scale up with the dosing of E2 creams similarly to what is seen with gels and patches (see graph,* **lower right***).*
- *As with E2 patches and gels, 0.7-1.8ng/mg may be the optimal target values for E2 when using the DUTCH Test. [See reference:* **28***]*

EXECUTIVE SUMMARY

Millions of women have navigated the menopause transition with the help of their healthcare practitioners. The decision to use menopausal hormone therapy, predominantly estradiol, is not as straightforward as one would hope. The WHI publications, with their confusing and often incorrect interpretations, coupled by all the media hype, has led many physicians and patients to avoid estradiol replacement therapy (ERT) and its documented beneficial effects.

Given the importance of this topic, it is surprising and frustrating how little data is available to answer some critical unanswered questions. For example, there are no randomized, double- blind, placebo-controlled, long-term studies that assess different estradiol forms, all three testing modalities (serum/urine/saliva), and clinical outcomes. The data necessary to properly navigate questions surrounding appropriate testing and treatment is offered in a fragmented way, scattered throughout the scientific literature.

This document represents a thorough, up-to-date literature review. While many studies using E2 patches and alcoholic gels were found, we were able to find just one peer-reviewed article reporting serum values following the application of a compounded estradiol cream.27 This study did not include clinical information, so there is presently no study evaluating transdermal estradiol creams' clinical efficacy and/or safety. We were also unable to find a single peer-reviewed reporting of any saliva data following TD E2 patches, gels, or creams. There are informal, non peer-reviewed data available.25, 26

Unlike E2 patches and alcoholic gels, there are no outcome studies to prove E2 creams are clinically effective or effectively monitored. There are also no peer-reviewed salivary studies that evaluate E2 creams. This lack of salivary peer-reviewed data creates difficulty in comprehensively reviewing TD E2's use and monitoring. This document is an attempt to encourage best practices for practitioners regarding all TD E2 products. Despite the lack of data for some key points, we have assembled guidance by comprehensively reviewing the available studies.

What do we know about the clinical utility of TD E2 products?

- Clinical data exists to evaluate effective doses for E2 patches and gels, but not for compounded creams.
- While incomplete, significant clinical data exists to evaluate estradiol therapy's benefits and risks.
- TD E2 patches and alcoholic gels show improved risk profiles compared to oral E2.

What do we know about lab testing to monitor TD E2 products?

- Serum data has been the gold standard against which all other testing modalities are compared.
- Serum data is published for commonly available E2 patch and gel doses, but not for creams.
- Data showing equivalence between serum and urine E2 testing is published (in various publications) on patients not using hormonal therapy. This includes a recent peer-reviewed publication showing DUTCH equivalencewith serum E2.29
  - Postmenopausal serum levels (approximately 0-20pg/mL) equate to 0.2-0.7ng/mg E2 in DUTCH testing.

- Published data shows urine and serum equivalence when using TD E2 patches.32 Similar research is needed for E2 gels and creams.
- DUTCH internal studied data shows a parallel pattern with published serum data for E2 patches and gels.
  - When using ERT, a commonly suggested serum range is 20-60pg/mL. This may equate to 0.7-1.8ng/mg for DUTCH.
- Available saliva data (non-peer reviewed publications) shows that compounded E2 cream doses as low as 0.25mg/d push saliva levels above premenopausal ranges.25, 26

Can we rely on testosterone (T) data to help us understand this topic more completely?

Transdermal T gels have been proven to increase serum in a linear, dose-dependent manner behaving similarly to transdermal E2 gels, which also drive serum up linearly. When common doses are used, both hormones significantly change serum levels. If the two hormones behave similarly, data regarding T may help fill in some of the gaps regarding TD E2. While expected salivary results have been published when monitoring E2 patches and compounded creams, no published data was found regarding concentrations with the use of transdermal E2 gels.

We know the minimal dose of E2 gels for clinical impact (see Table #1). Evaluating salivary values at these minimally effective doses would be extremely helpful, but the salivary data does not appear to exist. Can we assume that salivary values are similarly elevated with E2 gels as they have been proven to be with TD creams? Anecdotally it has been reported that salivary values do in fact increase to supraphysiological levels with the use of E2 gels as is reported regarding E2 creams in Table #3. Testosterone data confirms the parallel rise in saliva whether using a cream or gel. Transdermal T gels and creams (30-60mg) are both reported to increase saliva measurements to supraphysiological levels, far exceeding levels seen in patients not taking HRT.25,31 Testosterone also provides us with one published comparison of serum results when using creams and gels. Both products increased serum T levels, but twice as much T had to be used in the cream to match the serum level from the gel.30

It can be assumed (though not proven with published scientific data) that E2 taken as either an alcoholic gel or a compounded cream will increase salivary levels to supraphysiological levels with commonly used doses (0.25-1.0mg). As is detailed in this document, supraphysiological levels at these relatively low doses of transdermal E2 gels contradicts the modest clinical impact seen from these products.

QUESTION

Does transdermal progesterone (Pg) behave similarly to T or E2? As stated above, common doses of TD T and E2 increase serum and urine levels meaningfully. Most reported data regarding TD Pg shows, and DUTCH data confirms, very little change with doses as high as 100mg. This contrast should serve as a warning when extrapolating Pg.

LAB TESTING FOR THE MONITORING OF TRANSDERMAL (TD) ESTRADIOL (E2)

Lab testing for E2 patch monitoring is straightforward and intuitive, while E2 gels and creams can be more confusing. The highest commonly used E2 patch dose is 0.1mg/d. This dose will typically increase serum, urine, and saliva results from a postmenopausal norm to a premenopausal norm (follicular norms with moderate dosing and luteal levels if using higher doses).20,21,25,28,32 This makes sense. Confusion comes with gels and creams, which result in exaggerated salivary concentrations that dramatically contradict serum/urine levels.

When the highest commonly used FDA-cleared E2 gel doses are used, serum and urine respond similarly to patches,25,26 increasing to a premenopausal norm.2,12,28 Available data implies that E2 creams behave similarly,28 also increasing urine (DUTCH) concentrations to premenopausal luteal levels. When using saliva testing, E2 cream doses that gently lift serum and urine levels moderately, increase saliva levels well beyond the premenopausal ranges.25,26,27,28

To give a specific example, a 1.0mg/d E2 dose from a compounded E2 cream generally increases urine to a premenopausal norm (though the response is product-specific), like a 0.1mg/d patch.28 This 1.0mg/d dose of an E2 cream usually increases salivary results way outside of the premenopausal range (>5 times higher than levels seen when using a 0.1mg/d E2 patch; see saliva data on previous page).25,26 This does not make sense.

Either the serum/urine response to E2 gels and creams dramatically underrepresent tissue exposure, or salivary results greatly overestimate tissue burden.

QUESTION

Do gels and creams really contain much more E2 than patches (often >1mg compared to 0.0250.1mg)?

Patches are named for their effective daily doses, and gels and creams are named for how much E2 is in the dose (not how much absorbs). Some 0.1mg/d patches have 20mg of E2 in a single patch! Only a small fraction is absorbed daily.

MAKING SENSE OF THE DATA

Low-dose E2 patches deliver 0.025mg/d and contain up to 5mg of actual E2. They are typically switched out twice per week. Daily absorption is about 2-10% depending on the product.19,23 Increased serum, urine, and saliva concentrations are consistent with this interpretation.19,25,32 E2 gel products that are considered the lowest effective dose contain 0.25-1.5mg/d of E2 (actual amount is product specific). Serum and urine imply that daily absorption of gels and creams (limited data) are also low (<10%), compared to patches.3,10,28 The ovaries make 0.1-0.3mg of E2 per day, and 0.5 - 1.0mg E2 cream doses often push women's salivary levels beyond premenopausal norms.

Do serum and DUTCH results correlate?

- **Without Therapy:** YES! Published results have proven this.29
- **With E2 Patches:** Yes, urine and serum data has been published.32

- **With E2 Gels:** This has not been proven with concurrent measurements but the trends agree and suggest that serum and urine results correlate.
- **With E2 Creams:** More research is needed. Only one reference found reports serum values for compounded E2 creams.27

This means that saliva results suggest absorption rates closer to 100% when using creams and gels.28 If this is correct, much lower doses would be clinically effective. How do we know which lab values give us accurate information when monitoring E2 creams and gels?

We have searched the scientific literature to see if clinical changes following therapy agree with the moderate increases in serum/urine levels or the supraphysiologic salivary responses. The following is a list of clinical endpoints that have been studied at different patch and gel doses with concurrent serum measurements:

- Reduction of vasomotor symptoms (VMS)
- Increase in bone mineral density (BMD)
- Improvement in vulvovaginal atrophy (VVA)
- Endometrial thickening
- Increases in SHBG as a sign of hepatic estrogen exposure
- Suppression of FSH production as a sign of estrogen exposure in the brain (anterior pituitary)

Of the clinical parameters listed above, VMS, BMD, and VVA have been studied with placebo controls and are given prominence in this comparison. The other three parameters will be discussed briefly in the appendix of this document.

QUESTION

If you predicted clinical outcomes based on serum or urine numbers, predictions would be reasonably like the actual outcomes of clinical studies for E2 gels. If salivary values are used to predict outcomes, estimations of actual clinical success with E2 creams may be dramatically overestimated.

We have conceptually overlaid therapy-induced changes with serum, urine, and saliva concentrations along with concurrent clinical changes from various studies (tables #1, #2). The tables offer a summary of published serum levels and available clinical data regarding vasomotor symptoms (VMS), bone mineral density (BMD), and vulvovaginal atrophy (VVA) with different doses of patches and gel products. Because salivary results are exaggerated with creams (and presumably gels) and not patches, data is divided into separate tables. Do salivary results best represent the clinical reality? If so, the three doses (low, moderate, high) of E2 gel products should result in examples of higher E2 exposure relative to the three E2 patch doses. The collective observations of the listed studies in tables #1 and #2 contradict this conclusion. In fact, E2 gel products show multiple signs of lower E2 exposure when compared to the three E2 patch doses.

The clinical impact of the products listed in both tables is in alignment with serum levels (which generally correlate with urine values), not the exaggerated salivary E2 levels. Pro-saliva arguments have suggested that salivary values act as a surrogate for other tissue types in the body, making it a uniquely valuable clinical tool. A better interpretation may be that there exists some unique conduit between the skin, lymphatic system, and salivary

gland resulting in high salivary hormone concentrations that differs from other tissues. The elevation in saliva is most extreme with progesterone, the most lipophilic of the hormones, suggesting that subcutaneous fat may also play a role in hormone transport to the saliva gland. Ultimately, the unique nature of salivary results, when using TD hormones, may render the results intellectually puzzling and interesting, yet without clinical utility.

Table #1 shows why E2 patch products are popular. Patient responses, when compared to placebo groups, show significant improvements across multiple clinical parameters. Even with an ultralow-dose patch (0.014mg/d) that increased serum levels to just 8.6pg/mL, Ettinger found improved BMD.16

Table #2 shows FDA-approved non-patch products. E2 product manufacturers have chosen variable doses for their lowest dose. Most scale the dose up by 100% and 200% for their mid-level and high-level products, respectively. It is unknown if the doses are selected based on clinical response or serum levels.

QUESTION

A word about serum E2 methods:
Normal ranges for premenopausal and postmenopausal serum E2 levels are method dependent, so ranges vary from one lab to another. Most notably, immunoassay methods (EIA) provide less accurate measurements at low levels, resulting in much higher postmenopausal measurements. LC-MS/MS measurements are lower and are thought to be more accurate. For example, the postmenopausal range for Lab Corp EIA is 0-54.7pg/mL and only 0-15pg/mL with their LC-MS/MS method. This creates confusion and misinterpretation when examining the literature as methodologies are not always well defined.

A consistent pattern that emerges is a delayed (taking longer than higher doses to take effect) or a failed clinical response with the lowest doses. These failures or delays were all eliminated as the dosing scaled up. For example, the first low-dose gel products listed did not eliminate VMS at 4 weeks, taking longer than the higher dose options for each product. The EstroGel 0.27mg/d low-dose option, in which vaginal symptoms were studied, failed to show clinical impact. These delays and failures were not seen with the higher doses. With E2 patches, even the low-dose options succeeded where the low-dose gels were delayed or failed. This suggests these “low-dose” gel products are likely delivering low E2 doses even if salivary values are very high.

One could generalize from the data that if serum levels are not increased above ~20pg/mL, reduced clinical impact will be seen from these FDA-approved E2 gels. For bone mineral density an even higher level may be necessary (>~30pg/mL), although there is mixed data on this point.24 This does not necessarily mean that all patients should be dosed at these higher levels. Individual patient treatment must consider all relevant facts and risks including the potential risks of too much E2 tissue exposure. The larger point made by this data is that the changes in serum appears to accurately reflect clinical changes with therapy.

Salivary results suggest that when a cream or gel contains 0.3-0.5mg in a daily dose, much more hormone is delivered compared to even the highest TD E2 patch doses.25,26 The

clinical data does not support this conclusion. Overall, the clinical data and serum results seem to align, implying that estradiol gel low-dose products are indeed "low." Salivary results suggest that commonly used E2 gel and cream doses may be producing harmful, massive E2 tissue levels. There does not appear to be any current data to corroborate this implication.

EstroGel data are particularly revealing. Archer noted that when menopausal women used the 0.27mg/d gel, the dose was clinically insufficient. Vasomotor symptom relief was delayed (> 4 weeks for symptom relief) and vaginal symptom relief failed at this dose.1 The manufacturers recommend a minimum dose of 0.75mg/d.10 While this dose improved VMS and VVA symptoms without delay, improvements to bone mineral density showed a delayed effect (success at 12 months compared to 6 months with higher doses).12 At the doses that drove serum levels higher than 40pg/mL, success was seen at all time points for all clinical measurements (vasomotor, bone mineral density, and vaginal maturation). When considering VMD, BMD, and VVA, low-dose patches (0.025mg/d) showed improved performance compared to EstroGel 0.75mg/d doses and below.1,12

The consensus of the scientific literature reports the expectation of menopausal symptom relief, when using gels, at approximately 20pg/mL for serum E2, and increased bone mineral density at serum levels higher than 30-40pg/mL (lower levels have been shown to be successful using E2 patches).16,24 For the E2 gel products in table #1, these suggested thresholds overlap accurately with reported serum levels. As EstroGel doses scale up, serum levels scale linearly. Clinical impact parallels the serum increases intuitively. Available data suggests that urine results agree with this relationship28 and saliva contradicts it, though there is no published data confirming either for a specific gel product.

For the transdermal E2 products evaluated, serum and urine testing can be used to accurately monitor therapy. Serum testing should be performed using LC-MS/MS (or a similarly sensitive assay) for accurate testing at low levels. Concentrations ranging from 20-60pg/mL typically result in clinical success that seems to scale up with results. DUTCH estradiol results from 0.7-1.8ng/mg may be targeted as an approximately similar range. Practitioners should determine target values for individual patients based on clinical symptoms and risk concerns. As E2 levels increase there may be a concurrently increasing breast cancer risk, and this should be factored into appropriate dosing and lab values.

QUESTION

What about urine estrogen metabolites? For all situations in which transdermal E2 products are used, monitoring estrogen metabolites with DUTCH testing is advised. Corrective action may be considered when patient metabolism prefers the potentially carcinogenic 4-hydroxy metabolites (4-OH-E1, 4-OH-E2) and/or when methylation (conversion of hydroxy to methoxy estrogens) is poor.

Transdermal E2 Patch Best Practices

Daily dosing as low as 0.014mg/d has been shown to improve VMS, BMD, and VVA with serum levels as low as 8.6pg/mL.16,17,18 Higher dosing has proven to continue to improve symptoms at the expense of increased estradiol tissue exposure. A potentially concomitant increased breast cancer risk with higher E2 exposure must also be considered. Patches

seem to provide more consistent clinical results at lower serum levels (possibly due to less variable results throughout the day) compared to E2 gel products. Pushing serum E2 above 30-40pg/mL increases overall E2 exposure and may be unnecessary in most patients. Urine results between 0.7-1.8ng/mg are likely enough for symptom improvement.

Saliva testing has the potential to monitor patches effectively only if a commercially available method is proven to correlate with serum levels. As of the publication of this document, such a test does not exist.

Transdermal E2 Gel Best Practices

In order to achieve the same level of clinical success observed with the low-dose patches (.025mg/d), moderate E2 gel doses (i.e. EstroGel 0.75mg/d) are typically required. These doses generally push serum results to the 30-60pg/mL range, which may correlate to about 1.0-2.0ng/mg for DUTCH testing. In a research setting, multiple serum E2 measurements are often made with average serum results used to prove clinical correlation. In clinical practice, one value is typically used. An up-anddown pattern throughout the day is observed with most products, unlike when using E2 patches.10,20 DUTCH testing may be preferred for gel products due to the potential for serum results to show peaks or valleys throughout the day. Urine testing averages out these up-and-down patterns and may be less variable than serum testing.

Transdermal E2 Cream Best Practices

More research is needed. None of the FDA-approved products are best described as "creams." Compounding pharmacies may provide E2 creams, many of which also include estriol (E3) and other hormones. Nearly 100 scientific references discussing E2 gels and/or patches are available in the scientific literature. Only one such reference was found referring to a compounded E2 product. Sood reported serum concentrations following the application of the Vivelle-Dot E2 patch (top, solid line on graph to the right) and three different concentrations of compounded biest (estriol [80%] and estradiol [20%]). The top dashed line represents serum data (E2 serum concentrations in pg/mL can be seen on the Y-axis) when using 0.6mg/d of E2 (Biest 3.0mg). The bottom two lines represent 0.5mg/d and 0.4mg/d of E2.27 This data puts this product in line with the E2 gel products, though serum levels are lower than the best absorbed gel products, such as Divigel.3

As a reminder, this is the only available peer-reviewed research evaluating compounded E2 products, and it does not include any clinical data. Do these compounded products decrease VMS and increase BMD? Do clinical changes align with serum and urine concentrations as they do with E2 gels and patches? These questions remained unanswered for compounded E2 products.

QUESTION

> *If women with a uterus use ERT, adequate progesterone (Pg) must be given to protect against endometrial proliferation (200mg oral Pg is a proven treatment with standard ERT dosing).*

The data on the next page also shows how variable serum results can be throughout the day with E2 cream products. Many practitioners have anecdotally observed a lack of serum increase with compounded E2 creams. This data shows the potential for relatively low levels

when testing is not performed at a specific time following therapy. Because of the potential variability in serum data, and the consistency seen on the DUTCH test when comparing aggregate E2 gel and E2 cream data (see graph on page 5), DUTCH data may be preferred when testing E2 creams as it represents a better 24hour average. We may assume that changes to serum or urine E2, due to the use of a compounded E2 cream, will bring about similar clinical changes observed from the use of E2 gels. But this assumption has yet to be proven. Research is needed in this area!

CONCLUSION

Lab testing that best represents systemic exposure is the goal of hormone therapy monitoring. There is a wealth of scientific literature assessing transdermal estradiol's effects on menopausal comorbidities (VMS, BMD, VVA). These clinical changes correlate with changes in serum levels. Observed exaggerated salivary results, do not parallel clinical impact.

The only scenario in which supraphysiological hormone concentrations were identified at tissue levels was when hormone was applied directly to an area, such as the breast. Chang, as an example, placed progesterone (25mg) and estradiol (1.5mg) in an alcoholic gel directly on the breast. Not surprisingly, this resulted in breast tissue concentrations with dramatically higher hormone levels, upon biopsy. In this scenario, serum E2 increased slightly as expected, and serum progesterone remained unchanged.43 Serum and urine will reflect systemic exposure in these types of scenarios, but lab testing will not help in evaluating how much hormone has diffused directly into localized tissue. It is critical that we understand the utility and limitations of all laboratory testing in optimizing patient care.

When considering the totality of available data, monitoring E2 patches with serum or DUTCH testing is optimal. When considering E2 gels and creams, the DUTCH test may prove to be the most reliable. It has been shown to correlate to serum values (without therapy)29 and is less vulnerable to the daily up-and-down concentrations seen in serum. Additionally, our data shows levels that scale up intuitively with dosing for both gels and creams.28 Target DUTCH values of 0.71.8ng/mg may be most appropriate for ERT, but every patient should be treated on an individual basis. Serum testing can be used, but the timing of application and testing must be carefully considered with gels and creams. Saliva testing should never be used to monitor E2 creams or gels.

APPENDIX

This document has based its conclusions primarily on VMS, BMD, and VVA data, as they are the most comprehensively studied clinical endpoints. Additional clinical outcomes that have been investigated follow:

Endometrial Thickening

As estrogen concentrations increase, there is a proportional response in endometrial growth. An endometrial stripe that measures 2.3-5.1mm is normal for a postmenopausal woman. When using 0.05mg/d patches, Exacoustos reported significantly thicker endometrium from the E2 therapy.33 Conversely, doses as high as 1.0mg/d of Divigel were

reported, showing no significant increase in endometrial thickness over the 15-week trial period.3

Saliva E2 numbers with 1.0mg/d of a cream are typically at least 5 times higher than when women are on a 0.05mg/d E2 patch.25 If these values properly represented the endometrium, its thickness would be expected to exceed the patch data when using relatively low doses of these products. It seems a better interpretation that the saliva E2 exposure is higher than endometrial exposure, which is consistent with studies of other tissue.

SHBG

Goodman reported that multiple studies have shown slight increases in SHBG with a 0.05mg/d patch.34 SHBG is a very sensitive marker of excessive hepatic estrogen exposure.35 When oral estrogen is used, the liver is flooded with excess estrogen (first-pass effect) and SHBG levels increase dramatically. Salivary E2 results imply that use of 0.5-1.0mg/d of transdermal E2 creams or gels would create a significant E2 excess at the tissue level.25,26 EstroGel doses as high as 3mg/d have been shown to make no change to SHBG levels.35,36 This implies that the tissue excess in saliva may be unique to that tissue, and the liver likely does not have a similar increase. As is evidenced by stable SHBG levels, salivary levels cannot be extrapolated to other tissues.

FSH Suppression

Callejon showed that FSH levels decreased from 64 to 40mUI/mL with 1mg/d of an alcoholic E2 gel (<40% decrease).37 Studies using 0.05mg/d patches show this degree of FSH suppression at moderate serum levels.24 Why do transdermal E2 gels not suppress FSH to a greater degree? Likely because serum (and not saliva) results best represent the brain's E2 exposure. Luteal serum levels typically suppress FSH more than 50%, and salivary levels greatly exceed luteal saliva ranges when using TD E2 1mg/d as used in Callejon's study.25,26,37

Lipids (LDL, Triglycerides)

Transdermal estrogens are reported to lower both LDL and triglycerides. Transdermal E2 gels decrease these markers less than or equal to that observed when using E2 patches. Casanova used EstroGel 1.5mg/d and showed no significant change in triglycerides and a 5.6% decrease in LDL.38 Karjalainen, using Divigel 1mg/d, reported similar findings with an 8.5% decrease in LDL and no change in triglycerides.39 Both authors went on to correlate the change in LDL with the change in serum E2. It seems the increase in systemic E2 exposure from transdermal application improves the LDL-lowering effects. This shows the clinical utility of serum testing. It also creates a scenario that allows for a clinical comparison between these E2 gel doses and similarly tested patches.

Estraderm 0.05mg/d patches perform similarly in reducing LDL (Adami,40 12% decrease; Wakatsuki,41 3.4% decrease; Sendag,42 9.3% decrease) and appear to lower triglycerides more effectively (11%, 20%, 21% decreases for Adami, Wakatsuki, and Sendag, respectively) than gels. Estraderm 0.05mg/d patch, Divigel 1.0mg/d, and EstroGel 1.5mg/d all report serum values around 60pg/mL with changes in lipid levels.3,10,23 Using these gel products does not seem to exceed the estrogenic impact seen with the patches. The high level of tissue E2 exposure suggested by elevated salivary E2 concentrations, does not appear to extrapolate to systemic exposure from these studies.

MINIMAL TD E2 THERAPY FOR CLINICAL IMPACT

The most important goal is to use the lowest effective TD E2 dose, limiting total estrogen exposure, to achieve the desired outcome while minimizing risks.

Vasomotor Symptoms (VMS)

TD E2 is the treatment of choice. Both patches and gels work, although low dose (0.025mg) patches relieved VMS at earlier time points compared to most low dose gel products.

Patches

- Ultralow-dose (0.014mg/d), low-dose (0.025mg/d) and higher doses all relieve VMS within 4 weeks of initiating treatment.

Gels

- Low-dose Estrogel (0.27mg/d), Divigel (0.25mg/d), Elestrin (0.52mg/d), and Evamist (1.53mg/d) all relieve VMS (serum = 11-20pg/mL) but not until >4 weeks of use.
- Higher-doses of each gel relieves VMS at higher serum E2 levels within 4 weeks.
- Bone Mineral Density (BMD)

Osteoporosis

The most prevalent bone disorder, affects 30% of postmenopausal women in the USA.

Patches

- Ultralow-dose (0.014mg/d), low-dose (0.025mg/d), and higher E2 patch doses all significantly increased bone mineral density (BMD) with BMD continuing to increase as the dose is increased.
- For doses 0.025mg/d and higher, BMD is proven to increase at 6 and 12 months.
- The ultralow-dose (0.014mg/d) has been shown to improve BMD at 12 and 24 month but was not reported at 6 months.

Gels

- Estradiol gel preparations are not FDA approved for osteoporosis prevention.
- EstroGel (0.75mg/d) has been shown to increase BMD, at 12 months but not at 6 months.
- EstroGel (1.5mg/d) increases BMD at both 6 and 12 months.

Vulvovaginal Atrophy (VVA)

Estrogen therapy, unless otherwise contraindicated, is the gold standard for moderate to severe vulvovaginal atrophy and its associated symptoms.

Patches

- Ultralow-dose (0.014mg/d), low-dose (0.025mg), and higher doses all significantly decreases VVA symptoms and increases vaginal maturation index (VMI).

Gels

- Ultra-low dose EstroGel (0.27mg) failed to decrease VVA symptoms and improve VMI as it was insufficient E2 for clinical change.
- Low-dose Elestrin (0.52mg/d) and EstroGel (0.375mg/d) significantly decreases VVA symptoms and improves VMI.

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