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A Review on Changing Trends of Hormonal Replacement Therapy by Transdermal Estrogen Sprays in Post Menopausal Vasomotor Symptoms

	
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ABSTRACT

The post menopausal vasomotor symptoms are major problem associated with woman's healthcare. The symptoms include night sweats, hot flushes, insomnia, fatigue, depression, decrease cognitive function. Previously hormonal replacement therapy was administered orally but there are so many problems were associated with oral therapy like breast cancer, Cardiovascular complications. But now days some new therapy and innovation comes like transdermal patches, transdermal gels, transdermal creams to overcome the problem associated with oral hormonal replacement therapy. As per as patient compliance is concern FDA has approved most innovative therapy i.e transdermal sprays which is more convenient and offers certain advantages over other transdermal therapies.



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INTRODUCTION

Menopause is defined as the permanent cessation of menstruation due to the loss of ovarian activity, and technically occurs twelve months after the last menstrual cycle.

Women who are more than twelve months past their last menstrual period are said to be in postmenopause. During the postmenopausal women suffer from post menopausal symptoms like hot flushes, night sweats, insomnia, fatigue, depression, decrease cognitive function.. In order, to treat VMS hormonal replacement therapy i.e. replacement of hormone estrogen is preferred or in combination with progesterone. Previously hormone replacement was prescribed by oral route but there are several problems associated with oral therapy like breast cancer, cardiovascular complications hence in order to overcome these problems, transdermal therapies were designed But now a days by considering patient compliance FDA has approved estrogen in spray form which is very convenient and easy for application and offers certain advantages as compare to other transdermal therapies. This spray form of hormonal replacement therapy is most innovative concept and completely changing the conventional trend of therapy.

Content

Benefits of Hormonal Replacement Therapy

Reduction in vasomotor symptoms

- HRT is the most effective treatment at reducing vasomotor symptoms.
- Vasomotor symptoms are usually improved within four weeks of starting treatment and maximal benefit gained by three months.
- There has been shown to be a significant mean reduction in the frequency of hot flushes by around 18 per week and in the severity of hot flushes by 87 % compared with placebo^[1].

Improvement in quality of life

- HRT may also improve sleep, muscle aches, pains and quality of life in symptomatic women^[3].
- Short-term HRT may improve mood and also depressive symptoms.

Improvement of urogenital symptoms

- Various studies have shown that HRT significantly improves vaginal dryness and sexual function.
- HRT is effective in improving the symptoms related to vaginal atrophy^[4].
- HRT may also relieve the symptoms of urinary frequency, as it has a proliferative effect on the bladder and urethral epithelium^[2].
- Topical estrogen is very effective in improving urinary symptoms in menopausal women.^[5]
- Vaginal symptoms are improved, vaginal atrophy and pH decrease and there is improved epithelial maturation with topical estrogen preparations compared to placebo or non-hormonal gels^[6].

Reduction in osteoporosis risk

- HRT is effective in preserving bone mineral density.
- Taking HRT leads to a reduction in osteoporosis in the spine and hip^[7].
- Women taking HRT have a significantly decreased incidence of fractures with long-term use^[8].
- HRT is the first line treatment for the prevention and management of osteoporosis in women with menopausal symptoms who are under the age of 50 years.
- HRT should be considered in those women at high risk of fracture if there are no contraindications to HRT^[1].
- The bone protection qualities of HRT are dose-related.
- Although bone density declines after discontinuation of HRT, some studies have demonstrated that women who take HRT for a few years around the time of the menopause may have a long-term protective effect for many years after stopping HRT^[9].

Reduction in cardiovascular disease

- The relation between HRT and cardiovascular disease is controversial, but the timing and duration of HRT, as well as pre-existing cardiovascular disease, are likely to affect outcomes^[1].
- The Women's Health Initiative (WHI) trial demonstrated that there was a small increase in the incidence of coronary heart disease in the first year after starting HRT (women in this

trial were taking conjugated equine estrogens with or without medroxyprogesterone acetate)^[10].

- Women who start HRT when they are aged over 60 years have an increased risk of coronary heart disease.
- A recent study has shown that HRT reduces the incidence of coronary heart disease by around 50 % if it is started within ten years of the menopause^[11].
- This study also demonstrated that women receiving HRT early after menopause had a significantly reduced risk of mortality without any apparent increase in risk of cancer, venous thromboembolism (VTE) or stroke.
- Another RCT showed that there is a neutral impact on cardiovascular disease risk markers (eg. coronary calcium scores and intima thickness) in women who were given low-dose HRT within three years of their last period^[12].

Other benefits

- HRT has a protective effect against connective tissue loss and may even reverse this process^[13].
- Some studies have shown an improvement in cognition in women who started HRT in early menopause; others have not shown this benefit^[14].
- There is a possible reduction in the long-term risk of Alzheimer's disease and all cause dementia in those women who take HRT.
- However, further studies are needed to be undertaken in this area^[15].

Risk associated with Hormonal Replacement Therapy

The principal risks of HRT are thromboembolic disease (VTE and pulmonary embolism), stroke, cardiovascular disease, breast and endometrial cancer, and gallbladder disease^[1].

Large studies, including the WHI and the Million Women Study (MWS), in the past cast concerns and controversy over the use of HRT^{[10][16]}.

However, data accumulated from the WHI and other studies over the past decade have shown that, in women with symptoms or other indications, initiating HRT near menopause will probably provide a favorable benefit: risk ratio^[17].

Venous thromboembolism (VTE)

- Oral HRT (combined estrogen and progestogen, and estrogen-only) increases the risk of VTE, pulmonary embolism, and stroke^[18].
- The risk of VTE is increased two to three times with oral HRT.
- These risks increase with age and with other risk factors, such as obesity, previous thromboembolic disease, smoking, and immobility.
- In healthy women aged less than 60 years, the absolute risk of thromboembolic disease is low and mortality risks from VTE are low.
- The type, dose and delivery system of both estrogen and progestogen influence the risk of thromboembolic disease.
- The VTE risk appears to be higher among users of estrogens plus progestogens than among users of estrogens alone. In addition, there is evidence for a deleterious effect of medroxyprogesterone acetate on VTE risk^[19].
- Current use of oral estrogens increases the risk of VTE, especially during the first year of treatment, but past users of hormone therapy have a similar risk as never-users. However, transdermal estrogens are thought to be safe with respect to thrombotic risk^[20].

Stroke

The risk of ischemic (but not hemorrhagic) stroke is unclear. However, the risk:

- Appears to be increased in women taking estrogen-only or combined HRT.
- Does not appear to be increased in women under 60 years old.
- Tibolone increases the risk of stroke (doubled) in women aged over 60 years.
- Transdermal estrogen appears to be associated with a lower risk of stroke.
- The effects of HRT on stroke may be dose-related and so the lowest effective dose should be prescribed in women who have significant risk factors for stroke.

Breast cancer

Combined HRT increases the risk of breast cancer. However, the absolute risk is small at around one extra case of breast cancer per 1,000 women per annum. The risk:

- Is greatest in lean women (BMI <25).

- Is similar in magnitude to the risk associated with late menopause, early menarche, null parity, and obesity.
- Is also similar in magnitude to drinking two to three units of alcohol daily.
- Returns to that of a non-user within five years of stopping HRT.
- In respect of mortality, is not significantly increased in an HRT user.

The risk of breast cancer with estrogen-only HRT is far less than with combined HRT:

- Most observational studies do not demonstrate an increased risk of breast cancer in women taking estrogen-only HRT for up to five years^[21].
- The incidence of breast cancer may not be increased with estrogen alone, in hysterectomised women.
- There is no evidence of an increased risk of breast cancer in women on HRT under the age of 50 compared with menstruating women of the same age.
- Combined HRT also increases breast density and the risk of having an abnormal mammogram.^[22] It is important that women are informed about this.

Data regarding the true effect of HRT on the incidence of breast cancer are still contentious.

Endometrial cancer

- Estrogen-only HRT substantially increases the risk of endometrial cancer in women with a uterus.
- The use of cyclical progestogen for at least ten days per 28-day cycle eliminates this risk.
- Tibolone does not increase the risk of either endometrial hyperplasia or endometrial cancer^[23].

Ovarian cancer

- Current data on the role of HRT and the risk of ovarian cancer are still currently conflicting.
- There is some evidence that there is an increased risk of ovarian cancer with the use of HRT^[24].
- The WHI study has been the only RCT studying the incidence of ovarian cancer and HRT and it concluded there was no increased risk^[10].

Colorectal cancer

- The WHI trial showed that colorectal cancer risk was reduced in women taking combined conjugated equine estrogens and medroxyprogesterone acetate^[10].
- However, some experts feel that their results do not actually support a clinically meaningful benefit for combined hormone therapy on colorectal cancer^[25].
- Other studies have demonstrated a reduction in risk of colorectal cancer with use of oral combined HRT^[26].

METHOD OF APPLICATION OF TRANSDERMAL SPRAY

Transdermal spray is sprayed on a small area of your arm, and the medication is invisible and dries quickly within two minutes. The spray contains applicator contains 56 sprays and can be used to deliver 1, 2 or 3 spray doses each day. Treatment with estrogen should be started at the lowest dose possible, and used only for as long as needed to provide relief of moderate to severe hot flashes associated with menopause. Your doctor can start you at the lowest dose (1 spray) and easily adjust your dose to 2 or 3 sprays to find the dose that works for you. The spray must be applied to inside the forearm between the elbow and wrist



Figure-1

Transdermal spray is available in a spray applicator that delivers a measured amount of estradiol to the skin with each spray (see Illustration 1).

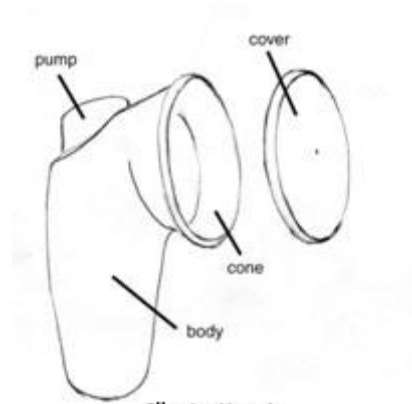


Illustration 1

1. Before using the applicator for the first time, it must be primed. With the cover on, and the applicator upright, fully depress the applicator three times with your thumb or index finger. This is called priming (see Illustration 2). After priming, the applicator is ready to use. The applicator should be primed only once when you first start using a new applicator. **DO NOT PRIME THE APPLICATOR BEFORE EACH DAY'S DOSE.**

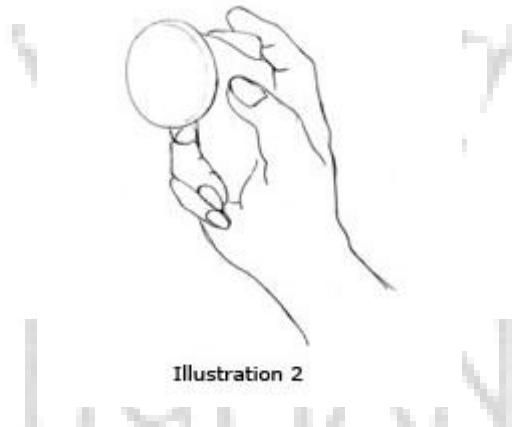


Illustration 2

2. Apply Transdermal spray once a day each morning.
3. Apply your daily dose of Transdermal spray to clean, dry, unbroken skin on the inside of the forearm between the elbow and the wrist (see Illustration 3). Do not apply Transdermal spray to other areas of the skin. To apply the dose, remove the plastic cover, hold the applicator upright and rest the plastic cone flat against the skin. You may need to change the position of your arm or the position of the cone on your arm so that the cone is flat against your skin and there are no gaps between the cone and your skin. Depress the pump fully once.



Illustration 3

4. If your healthcare provider tells you to increase the dose to 2 or 3 sprays, you should move the cone before applying the second or third spray to an area of the skin next to but not touching the area of the previous spray (see Illustration 4).

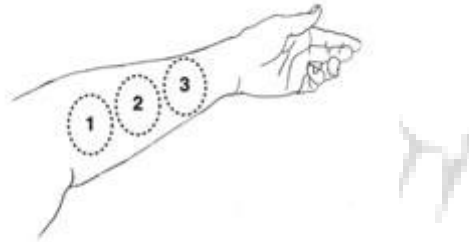


Illustration 4

5. Always place the protective cover back on the cone of the applicator.
6. Do not rub transdermal spray into your skin. EVAMIST spray should dry on your skin for at least 2 minutes before you get dressed, and at least one hour before you wash your skin.

After you spray transdermal spray on your skin, do not allow other people and pets to make contact with the area of skin where you applied the spray after application. Cover your skin with clothing where you sprayed transdermal spray if you think another person will come in contact with that area of skin. If you get transdermal spray on another area of your skin like your hands, wash that area of your skin with soap and water right away.

7. The estrogen in transdermal spray can transfer from the area of skin where it was sprayed to other people. Do not allow others, especially children, to come into contact with the area of your skin where you sprayed transdermal spray. Young children who

are accidentally exposed to estrogen through contact with women using transdermal spray may show signs of puberty that are not expected (for example, breast budding).

8. If another person accidentally touches the area of your skin where you sprayed transdermal spray, tell that person to wash the area of their skin with soap and water right away. The longer the transdermal spray stays on the skin before it is washed off, the greater the chance the estrogen hormone may be absorbed.
9. If a child under your care unexpectedly starts to develop breasts or has other sexual changes:
 - Have the child checked right away by their healthcare provider.
 - Talk to your healthcare provider about the correct use of transdermal spray when around children.
 - Stop using transdermal spray and call your healthcare provider right away if you see any signs and symptoms (breast development or other sexual changes) in a child that may have occurred through accidental exposure to Transdermal spray.

In most cases the child's breasts will go back to normal when they are no longer exposed to Transdermal spray.

Talk to you healthcare provider to discuss other treatments for your menopause symptoms if accidental exposure to Transdermal spray cannot be avoided.

10. Transdermal spray contains alcohol, and alcohol-based liquids are flammable. Avoid fire, flame or smoking when using transdermal spray until the spray has dried. Do not apply transdermal spray while standing near a flame.
11. Never apply transdermal spray directly to the breast or in or around the vagina. Start at the lowest dose (1 spray) and talk to your healthcare provider about how well that dose is working for you. Treatment with estrogen should be started at the lowest dose possible, and used only for as long as needed to provide relief of moderate to severe hot flashes associated with menopause. You and your healthcare provider should talk regularly (every 3-6 months) about the dose you are taking and whether you still need treatment with transdermal spray.

The transdermal spray applicator contains enough products to allow for initial priming of the pump with three sprays plus application for 56 sprays. The product will last

approximately 56 days if you use 1 spray each day, 28 days if you use 2 sprays each day and 18 days if you use 3 sprays each day.

Do not use this applicator for more than 56 sprays even though the bottle may not be completely empty.

Transdermal spray can be stored in a clean, dry place at room temperature (15° to 30°C or 59° to 86°F) and does not need refrigeration. Do not freeze. Transdermal spray should not be used after the expiration date. When the applicator has been used for 56 sprays you can discard it in normal household waste.

SIDE EFFECTS

Breast pain or tenderness; headache; mild fluid retention; mild hair loss; mild nausea or vomiting; spotting or breakthrough bleeding; stomach cramps or bloating.

Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue; unusual hoarseness); blurred or double vision, vision loss, or other vision changes; breast lump or discharge; calf or leg pain or swelling; chest pain; confusion; coughing up blood; fainting; memory problems; mental or mood changes (eg. depression) migraine headache; numbness of an arm or leg; one-sided weakness; persistent or recurring abnormal vaginal bleeding; severe or persistent headache or dizziness; severe or persistent stomach pain, nausea, or vomiting; shortness of breath; slurred speech; swelling of the hands, legs, or feet; vaginal discharge, itching or odor; yellowing of the skin or eyes.

CONTRAINDICATION

Transdermal spray may cause dizziness. This effect may be worse if you take it with alcohol or certain medicines. Use spray with caution. Do not drive or perform other possibly unsafe tasks until you know how you react to it.

Transdermal spray is for external use only. Do not get it in your eyes, nose, vagina, or mouth. If you get it in any of these areas, rinse right away with warm clean water.

Check with your doctor before you apply sunscreen to the application site while you are using Transdermal spray.

Transdermal spray is flammable. Avoid fire, flame, or smoking until the medicine has dried on your skin.

Eating grapefruit or drinking grapefruit juice may increase the risk of Transdermal spray's side effects. Talk to your doctor before including grapefruit or grapefruit juice in your diet while you are taking Transdermal spray.

Tell your doctor or dentist that you take Transdermal spray before you receive any medical or dental care, emergency care, or surgery. If possible, Transdermal spray should be stopped at least 4 to 6 weeks before surgery or any time you might be confined to a bed or chair for a long period of time (such as a long plane flight, car ride, bed rest, or illness).

Transdermal spray may cause dark skin patches on your face. Exposure to the sun may make these patches darker. If patches develop, use a sunscreen or wear protective clothing when exposed to the sun, sunlamps, or tanning booths.

If you wear contact lenses and you develop problems with them, contact your doctor.

Diabetes patients- Transdermal spray may affect your blood sugar. Check blood sugar levels closely. Ask your doctor before you change the dose of your diabetes medicine.

Transdermal spray may interfere with certain lab tests. Be sure your doctor and lab personnel know you are using Transdermal spray.

Talk with your doctor regularly (eg. every 3 to 6 months) about whether you need to continue taking Transdermal spray.

Lab tests and medical exams, including physicals and blood pressure, may be performed while you use Transdermal spray. You should have breast and pelvic exams, and a Pap test at least once a year. You should also have periodic mammograms as determined by your doctor. These tests may be used to monitor your condition or check for side effects. Be sure to keep all doctor and lab appointments.

Examine your breasts monthly as directed by your doctor. Report any lumps right away.

Use Transdermal spray with caution in the ELDERLY; they may be more sensitive to its effects.

Transdermal spray should not be used in CHILDREN; safety and effectiveness in children have not been confirmed.

PREGNANCY and BREAST-FEEDING: Do not use Transdermal spray if you are pregnant. If you think you may be pregnant, contact your doctor right away. Transdermal spray is found in breast milk. Do not breast-feed while you are taking Transdermal spray.

ADVANTAGES

This transdermal spray offers certain advantages over other transdermal therapies. It is more patient compliance therapy.

Transdermal therapy helps to give hormone replacement at low and effective dose of estrogen. Due to low dose possible side effects of estrogen get avoided. It provides uniform delivery of hormone for each time of application.

CONCLUSION

The hormonal replacement therapy in transdermal spray form is most innovative and novel method of estrogen administration. It is most convenient and patient compliant therapy for administration and also safer as per patient safety is concern. But it is very essential to give proper guidelines to patient for proper use of spray along with applicator.

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