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How does VTE risk for the patch and vaginal ring compare with oral contraceptives?

Evidence-based answer

Evidence is conflicting with regard to the comparative frequency of venous thrombotic events (VTE) among women using the transdermal patch when compared to an oral contraceptive (OC), even though the patch produces a relatively

high serum ethinyl estradiol (EE) level (strength of recommendation [SOR]: **C**, conflicting cohort case-control studies).

The vaginal ring has a risk of VTE comparable to that of an OC (SOR: **B**, 1 comparative study).

Clinical commentary

For now, base decisions on patient preference

This review points out that we don't have enough evidence to make a strong recommendation about oral or nonoral estrogen-containing contraceptives based on the risk of thromboembolic disease. All estrogen-containing contraceptives have similar side-effect profiles, regardless of the route of administration.

In my experience, the patch or

ring appeals to women who have had difficulty with OCs and need a simpler dosing regimen to improve compliance. The choice between an oral estrogen-containing contraceptive and the patch or ring should be based on the patient's preference, not the risk of thromboembolic disease, until we have evidence to suggest otherwise.

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FAST TRACK

All estrogen-containing contraceptives have similar side-effect profiles, regardless of the route of administration

Evidence summary

Two nonoral estrogen-progestin contraceptives have been approved by the US Food and Drug Administration (FDA). OrthoEvra is a transdermal patch applied weekly for 3 consecutive weeks, followed by 1 patch-free week per cycle.¹ The NuvaRing is a vaginal ring worn for 3 consecutive weeks in a 4-week cycle.²

The patch causes greater estrogen exposure than OCs or the ring

In November 2005, the FDA issued an

update to the labeling of the OrthoEvra contraceptive patch, reporting increased systemic estrogen exposure, which may increase the risk of blood clots.³ The FDA warned that the transdermal patch exposes the user to 60% more estrogen than the typical birth control pill containing 35 µg EE.³ In January 2008, the FDA approved an additional update to include the results of a new study that found users of the patch to be at higher risk of developing VTE than OC users.^{3,4}

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treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General, Changes in Height and Changes in Weight**). Should the decision be made to treat a pediatric patient with Effexor XR, the monitoring of weight and height is recommended throughout the course of treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Effexor XR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see **PRECAUTIONS: Hyponatremia**). **ADVERSE REACTIONS: Associated with Discontinuation of Treatment**—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. **Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD**—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. **Vital Sign Changes:** Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 3 beats/min in SAD trials. (see **Sustained Hypertension and Elevations in Systolic and Diastolic Blood Pressure** sections of **WARNINGS**). **Laboratory Changes:** Clinically relevant increases in serum cholesterol were observed in Effexor XR trials. Increases were duration dependent over the study period and tended to be greater with higher doses. **Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR**—N=7,212. "Frequent"—events occurring in at least 1/100 patients; "infrequent"—1/100 to 1/1000 patients; "rare"—fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, numbness, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis, granuloma. **Cardiovascular system** - Frequent: migraine, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cool feet and/or cold hands), postural hypotension, syncope; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia, thrombophlebitis. **Digestive system** - Frequent: indigestion, frequent burping, constipation, dysphagia, tongue edent, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distention, biliary pain, chelitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhea, gaster, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypochloremia, hypoglycemia, hyperlipidemia, hypernatremia, hypokalemia, SGOT increased, increased thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcemia, hyperkalemia, hyperphosphatemia, hyperuricemia, hypochlosteremia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteoclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradycardia, hyperreflexia, increased lacrimation, otitis, otitis media, parosmia, photophobia, taste loss, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating increased. **Sight, hearing, and taste** - Frequent: blurred vision, abnormal vision, mydriasis, taste perversions; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, otitis media, parosmia, photophobia, taste loss; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, hyperacusis, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis, visual field defect. **Urogenital system** - Frequent: albuminuria, urination impaired; Infrequent: amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, hemorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginitis. **Pre-marketing Reports:** acute myocardial infarction, anaphylaxis, aplastic anemia, ataxia, cardiac anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; toxic epidermal necrolysis/Sievens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation); abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methyphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tremors (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIAH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE:** Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE:** The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdosage. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR). **DOSE AND ADMINISTRATION:** Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR, Prescribing Information W10404C036 ET01, revised February 2008.

One pharmacokinetic study found that exposure to EE differed among delivery systems. The area under the EE concentration-vs-time curve in the patch group was 1.6 times higher than in the OC group ($P<.05$) and 3.4 times higher than in the vaginal ring group ($P<.05$).²

So what's the VTE risk? Two studies, contrasting conclusions

A nested case-control study—based on a PharmMetrics longitudinal database of information from paid claims by managed care health plans—included 215,769 women between the ages of 15 and 44 years who had started using the patch or a norgestimate-EE combination OC since April 1, 2002, when OrthoEvra was first introduced on the US market.⁵ Investigators identified 68 diagnosed cases of VTE with no identifiable risk factors.

The overall incidence of VTE in this study was 52.8 per 100,000 women-years (95% confidence interval [CI], 35.8-74.9) among patch users and 41.8 per 100,000 women-years among OC users (95% CI, 29.4-57.6).⁵ The study concluded that the risk of nonfatal VTE for the patch isn't higher than the risk for an OC containing 35 µg EE and norgestimate (odds ratio [OR]=0.9; 95% CI, 0.5-1.6; incidence rate ratio [IRR]=1.1; 95% CI, 0.7-1.8).

A recent update to the study evaluated an additional 17 months of data on new cases of VTE from the original study and the update show that the OR for VTE is 1.0 (95% CI, 0.7-1.5) in users of the patch compared with users of the OC.⁶

Another nested case-control study—based on UnitedHealthcare insurance claims data and confirmatory chart reviews—showed contrasting results. The study included 340,377 women between the ages of 15 and 44 years who were new users of the patch or new and previous users of a norgestimate-EE combination OC from April 1, 2002 through December 31, 2004.³ Investigators verified 57 diagnoses of VTE, controlling for confound-

ing factors. The incidence of VTE in this study was 40.8 per 100,000 women-years among patch users and 18.3 per 100,000 women-years among users of the norgestimate-35 µg EE OC. The study reported a more than 2-fold increased risk of VTE in patch users compared to OC users (OR=2.4; 95% CI, 1.1-5.5; IRR=2.2; 95% CI, 1.3-3.8).^{3,7}

Do the differences between studies make a difference?

The 2 studies appear similar in design but have 2 major identifiable differences:

- The first study verified VTE diagnoses by claims for systemic anticoagulants, whereas the second study expanded its analysis by performing confirmatory chart reviews for VTE diagnoses.
- The first study included only new OC and patch users as of April 1, 2002, whereas the second study included new and experienced users of the OC as of April 1, 2002.

The significance of the differences in these studies is debatable; the results have yielded controversial, conflicting evidence.

Safety and tolerability are similar for the vaginal ring and OCs

A 1-year, open-label, randomized Phase III study of 1030 women compared the NuvaRing with a combination OC containing levonorgestrel and 30 µg EE. One case of deep venous thrombosis occurred in the NuvaRing group.

In reviewing the data, the authors concluded that the NuvaRing demonstrated comparable safety and tolerability to the OC.⁸ NuvaRing users experienced similar side effects compared with OC users.⁹

Recommendations

The World Health Organization Medical Eligibility Criteria for Contraceptive Use (WHOMEC) reports that long-term safety data for the estrogen-progestin contraceptive patch are not available.¹⁰

However, the limited studies that are available suggest a safety profile similar to that of combination OCs with comparable hormone formulations.

WHOMEC suggests that the guidelines for combination OCs also should apply to the patch and the ring. Women shouldn't use these contraceptive methods if they have a history of VTE or current VTE or if they are undergoing major surgery that may include prolonged immobilization.¹⁰ ■

References

1. Abrams LS, Skee D, Natarajan J, Wong FA. Pharmacokinetic overview of Ortho Evra/Evra. *Fertil Steril*. 2002;77(2 suppl):S3-S12.
2. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception*. 2005;72:168-174.
3. US Food and Drug Administration Center for Drug Evaluation and Research. Ortho Evra (norgestromin/ethinyl estradiol) Information. Available at: www.fda.gov/cder/drug/infopage/orthoevra/default.htm. Accessed July 5, 2008.
4. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. *Obstet Gynecol*. 2007;109(2 Pt 1):339-346.
5. Jick SS, Kaye JA, Russmann S, Jick H. Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. *Contraception*. 2006;73:223-228.
6. Jick S, Kaye JA, Li L, Jick H. Further results on the risk of nonfatal venous thromboembolism in users of the contraceptive transdermal patch compared to users of oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. *Contraception*. 2007;76:4-7.
7. Burkman RT. Transdermal contraceptive patch. In: Rose BD, ed. UpToDate [online database]. Waltham, Mass: UpToDate; 2008.
8. Oddsson K, Leifels-Fischer B, de Melo NR, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. *Contraception*. 2005;71:176-182.
9. Gaffield ME, Curtis KM, Mohllajee AP, Peterson HB. Medical eligibility criteria for new contraceptive methods: combined hormonal patch, combined hormonal vaginal ring and the etonogestrel implant. *Contraception*. 2006;73:134-144.
10. Reproductive Health and Research, World Health Organization. *Medical Eligibility Criteria for Contraceptive Use*. 3rd ed. Geneva, Switzerland: World Health Organization; 2004. Available at: www.who.int/reproductive-health/publications/mec/mec.pdf. Accessed September 12, 2008.

FAST TRACK

The patient's preference should determine the choice between an estrogen-containing OC and the patch or ring