



GUEST EDITORIAL

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Why evidence-based guidelines on hormones aren't all alike

Medical evidence accumulates at a pace too fast for the individual mortal to absorb. Inevitably, trustworthy guidelines became essential to day-to-day decision-making, particularly regarding the use of estrogen and progesterone in peri- and postmenopausal women.

■ Frequent updates help interpret proliferating data

A Hormone Therapy Panel of experts in many fields was convened in each of the last 3 years by the North American Menopause Society (NAMS), to review new studies and determine whether recommendations need to be changed, in light of new issues and new evidence. These Position Statements have become the internationally recognized standard of care.

October 6, 2004, a new Position Statement was announced at the annual NAMS meeting in Washington, DC.

In theory, developing a Position Statement according to the principles of evidence-based medicine would seem simple. Identical databases and published evidence should lead to identical consensus statements and clinical guidelines, should they not? Why then do different organizations, after scrutinizing identical evidence, come out with different interpretations and recommendations?

For example, one of the most enduring debates is to what extent evidence based on a select population can be extrapolated

to another select population or to the general population. Argument about the populations studied in the Women's Health Initiative and the Nurses Health trials rages vociferously. Neither study is able to consider all the combinations and variations we encounter in practice.

We will always lack a complete database. It is impossible to undertake and complete evidence-based clinical research that incorporates all populations, subpopulations, conflicting and confounding factors, comorbidities, risk factors, and medication permutations.

■ Practical experience, judgment called into play

What's more, guideline development would be flawed were it to rely entirely on the existing base of evidence at any one time. Development of guidelines must accommodate the clinical and scientific judgment of both the developer and the clinicians who will put the recommendations into practice. The judgment element explains the differing guidelines, in considerable part.

We considered all of these issues as we wrote the new NAMS Position Statement on peri- and postmenopausal estrogen and progesterone usage. Like previous reports, the latest one identifies issues that cannot be resolved now because of insufficient data.

We invite you to scrutinize our latest

New Position Statement

■ **No stipulation on starting or stopping hormone therapy**

■ **Safety issues of "bioidenticals" same as for estrogen**

More key recommendations, page 13

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Position Statement. But translating these positions into practice still necessitates taking into account the complete health profile of the individual woman as well as her personal preferences and beliefs. This Position Statement is intended to enhance the quality of patient care and modulate clinical practice. NAMS believes the positions we have taken are fair and credible, and we hope that both you and your patients will find them practical and acceptable.

Ultimately, we have to do the best we can with what we know at the moment.



www.menopause.org

Recommendations

Consensus points in the new document include some retained from 2003 (*Menopause*. 2003;10:497–506).

Unresolved issues

The Expert Panel found that data were insufficient to answer these questions:

- *Should women who are doing well on long-term hormone therapy (HT) discontinue?*
- *Is there a best way to discontinue HT?*
- *Does a continuous-combined EPT regimen have an effect different from continuous estrogen with sequential progestogen?*
- *Is HT associated with early risk of coronary heart disease?*

DERMABOND*

Topical Skin Adhesive
(2-Octyl Cyanoacrylate)

INDICATIONS

DERMABOND and High viscosity DERMABOND Topical Skin Adhesive are intended for topical application only to hold closed easily approximated skin edges of wounds from surgical incisions including minimally invasive surgery, and simple, trauma-induced lacerations. DERMABOND and high viscosity DERMABOND adhesive may be used in conjunction with, but not in place of, deep dermal sutures.

CONTRAINDICATIONS

- Do not use on any wound with evidence of active infection, gangrene, or wounds of decubitus etiology.
- Do not use on mucosal surfaces or across mucocutaneous junctions (e.g., oral cavity, lips), or on skin which may be regularly exposed to body fluids or with dense natural hair, (e.g., scalp).
- Do not use on patients with a known hypersensitivity to cyanoacrylate or formaldehyde.

WARNINGS

- DERMABOND and high viscosity DERMABOND adhesive is a fast setting adhesive capable of adhering to most body tissue and many other materials, such as knuckles, elbows, or knees, unless the joint will be immobilized during the skin healing period.
- Polymerization of DERMABOND and high viscosity DERMABOND adhesive may be accelerated by water or fluids containing alcohol. DERMABOND and high viscosity DERMABOND adhesive should not be applied to wet wounds.
- DERMABOND and high viscosity DERMABOND adhesive should not be applied to the eye. If contact with the eye occurs, flush the eye copiously with saline or water. If residual adhesive remains, apply topical ophthalmic ointment to help loosen the bond and contact an ophthalmologist.
- When closing facial wounds near the eye with DERMABOND and high viscosity DERMABOND adhesive, position the patient so that any run-off of adhesive is away from the eye. The eye should be closed and protected with gauze. Prophylactic placement of petroleum jelly around the eye, to act as a mechanical barrier or dam, can be effective in preventing inadvertent flow of adhesive into the eye. DERMABOND and high viscosity DERMABOND adhesive will not adhere to skin pre-coated with petroleum jelly. Therefore, avoid using petroleum jelly on any skin area where DERMABOND and high viscosity DERMABOND adhesive is intended to adhere. Use of DERMABOND adhesive near the eye has inadvertently caused some patients' eyelids to be sealed shut. In some of these cases, general anesthesia and surgical removal has been required to open the eyelid.
- DERMABOND and high viscosity DERMABOND adhesive should not be used below the skin because the polymerized material is not absorbed by tissue and can elicit a foreign body reaction.
- DERMABOND and high viscosity DERMABOND adhesive should not be used in high skin tension areas or across areas of increased skin tension, such as knuckles, elbows, or knees, unless the joint will be immobilized during the skin healing period.
- DERMABOND and high viscosity DERMABOND adhesive treated wounds should be monitored for signs of infection. Wounds with signs of infection, such as erythema, edema, warmth, pain and pus, should be evaluated and treated according to standard practice for infection.
- DERMABOND and high viscosity DERMABOND adhesive should not be used on wound sites that will be subjected to repeated or prolonged moisture or friction.
- DERMABOND and high viscosity DERMABOND adhesive should only be used after wounds have been cleaned, debrided and are otherwise closed in accordance with standard surgical practice. Local anesthetic should be used when necessary to assure adequate cleansing and debridement.
- Excessive pressure of the applicator tip against wound edges or surrounding skin can force the wound edges apart and allow adhesive into the wound. Adhesive within the wound could delay wound healing and/or result in adverse cosmetic outcome. Therefore, DERMABOND and high viscosity DERMABOND adhesive should be applied with a very light brushing motion of the applicator tip over easily approximated wound edges.
- DERMABOND and high viscosity DERMABOND adhesive polymerizes through an exothermic reaction in which a small amount of heat is released. With the proper technique of applying DERMABOND and high viscosity DERMABOND adhesive in multiple thin layers (at least three) onto a dry wound and allowing time for polymerization between applications, heat is released slowly and the sensation of heat or pain experienced by the patient is minimized. However, if DERMABOND and high viscosity DERMABOND adhesive is applied so that large droplets of liquid are allowed to remain unspread, the patient may experience a sensation of heat or discomfort.
- DERMABOND and high viscosity DERMABOND adhesive is packaged for single patient use. Discard remaining opened material after each wound closure procedure.
- Do not resterilize DERMABOND and high viscosity DERMABOND adhesive.
- Do not place DERMABOND and high viscosity DERMABOND adhesive in a procedure pack/tray that is to be sterilized prior to use. Exposure of DERMABOND and high viscosity DERMABOND adhesive, after its final manufacture, to excessive heat (as in autoclaves or ethylene oxide sterilization) or radiation (such as gamma or electron beam), is known to increase its viscosity and may render the product unusable.

PRECAUTIONS

- High viscosity DERMABOND adhesive has not been evaluated for use on wounds such as surgical incisions, punctures from minimally invasive surgery.
- Do not apply liquid or ointment medications or other substances to the wound after closure with DERMABOND or high viscosity DERMABOND adhesive, as these substances can weaken the polymerized film and allow for wound dehiscence. DERMABOND and high viscosity DERMABOND adhesive permeability by topical medications has not been studied.
- DERMABOND and high viscosity DERMABOND adhesive permeability by fluids is not known and has not been studied.
- DERMABOND adhesive is a free flowing liquid slightly more viscous than water. High viscosity DERMABOND adhesive, as a liquid, is syrup-like in viscosity. To prevent inadvertent flow of liquid DERMABOND and high viscosity DERMABOND adhesive to unintended areas: (1) the wound should be held in a horizontal position, with DERMABOND or high viscosity DERMABOND adhesive applied from above, and (2) DERMABOND or high viscosity DERMABOND adhesive should be applied in multiple (at least 3), thin layers rather than in a few large droplets.
- Hold applicator away from yourself and the patient and break ampule close to its center one time only. Do not crush the contents of the applicator tube repeatedly as further manipulation of the applicator may cause glass shard penetration of the outer tube.

High Viscosity

DERMABOND*

Topical Skin Adhesive
(2-Octyl Cyanoacrylate)

- DERMABOND or high viscosity DERMABOND adhesive should be used immediately after crushing the glass ampule as the liquid adhesive will not flow freely from the applicator tip after a few minutes.
- If unintended bonding of intact skin occurs, peel, but do not pull the skin apart. Petroleum jelly or acetone may help loosen the bond. Other agents such as water, saline, Betadine® Antibiotics, HIBICLENS® (chlorhexidine gluconate), or soap, are not expected to immediately loosen the bond.
- Safety and effectiveness of DERMABOND and high viscosity DERMABOND adhesive on wounds of patients with peripheral vascular disease, insulin dependent diabetes mellitus, blood clotting disorders, personal or family history of keloid formation or hypertrophy, or burst stellate lacerations, have not been studied.
- Safety and effectiveness of DERMABOND and high viscosity DERMABOND adhesive on the following wounds have not been studied: animal or human bites, puncture or stab wounds.
- Safety and effectiveness on wounds that have been treated with DERMABOND and high viscosity DERMABOND adhesive and then exposed for prolonged periods to direct sunlight or tanning lamps have not been studied.
- Safety and effectiveness of DERMABOND and high viscosity DERMABOND adhesive on wounds in vermilion surfaces has not been studied.

ADVERSE REACTIONS

Adverse reactions encountered during the clinical study for closure of trauma-induced lacerations using high viscosity DERMABOND adhesive and the clinical study comparing low viscosity DERMABOND adhesive to sutures, staples, and adhesive strips are listed below.

The safety of both high viscosity DERMABOND adhesive and the low viscosity DERMABOND adhesive control was measured in a randomized clinical study of 84 patients, 42 patients receiving high viscosity product and 42 receiving low viscosity product, by 1) the presence or the extent of an inflammatory reaction, 2) the presence of signs of clinical infection, 3) cosmetic outcome at Day 30, 4) assessment of thermal discomfort, and 5) the reported adverse events associated with use of the device. No significant differences between the two treatment groups were observed for any of these safety outcome measures, although 17 patients (44%) randomized to the high viscosity DERMABOND adhesive treatment group experienced a sensation of heat during application of the skin adhesive compared to 10 patients (26%) randomized to the low viscosity DERMABOND adhesive treatment group. Of those 17 patients in the high viscosity group, 5 of the patients noted that sensation of heat was uncomfortable. None of the patients in the low viscosity group observed objectionable sensation of heat.

As indicated under WARNINGS, high viscosity DERMABOND adhesive polymerizes through an exothermic reaction in which heat is released. It is important to use the proper technique of applying high viscosity DERMABOND adhesive in thin layers to minimize the risk that the patient may experience a sensation of heat or discomfort. This is especially important in the application of high viscosity DERMABOND adhesive, because the increased viscosity of the product relative to low viscosity DERMABOND adhesive can create a thicker applied layer resulting in a higher potential for heat to be generated. High viscosity DERMABOND adhesive should always be applied in thin layers so that large amounts of liquid are not allowed to collect, resulting in thermal discomfort for the patient.

Adverse reactions encountered during clinical study comparing low viscosity DERMABOND adhesive to sutures, staples, and adhesive strips are listed in the table below.

Clinical Study Outcomes	No Subcuticular Sutures		With Subcuticular Sutures	
	DERMABOND N (%)	Control N (%)	DERMABOND N (%)	Control N (%)
Adverse Reactions				
Suspected Infection*	8 (3.6%)	2 (0.9%)	6 (3.6%)	2 (1.2%)
Wound type				
# Lacerations	8	2	1	0
# Incisions	0	0	5	2
Dehiscence with Need for Retreatment	6 (2.5%)	5 (2.1%)	3 (1.8%)	0
Erythema	26 (11.5%)	74 (33.0%)	52 (31.3%)	75 (45.1%)
Edema	22 (9.7%)	28 (12.5%)	62 (37.3%)	71 (42.8%)
Pain	14 (6.1%)	13 (5.8%)	56 (33.7%)	57 (34.3%)
Warmth	3 (1.3%)	6 (2.6%)	3 (1.8%)	4 (2.4%)

*In the clinical study, presence of infection was to be identified by observation of redness more than 3–5 mm from the repaired wound, swelling, purulent discharge, pain, increased skin temperature, fever, or other systemic signs of infection. (See clinical study). Confirmatory culture was not routinely obtained. Among cases of suspected infection for low viscosity DERMABOND adhesive, 7/14 (50%) were in patients less than 12 years old with traumatic lacerations; overall, 8 of the 14 (approximately 60%) low viscosity DERMABOND adhesive wounds with suspected infections were associated with sub-optimal cosmetic outcome.

- Reactions may occur in patients who are hypersensitive to cyanoacrylate or formaldehyde. See CONTRAINDICATIONS.
 - The polymerization of DERMABOND adhesive on the skin releases small amounts of heat which may cause a sensation of heat or discomfort in some patients.
 - Adverse reactions may be experienced following DERMABOND and high viscosity DERMABOND adhesive contact with the eye.
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on hormone therapy in peri- and postmenopause

New recommendations

Duration

- ET/EPT can be used for a time consistent with treatment goals and provided the patient is monitored regularly; there was no stipulation on when to reduce or stop therapy.

"Bioidenticals" have same safety issues as traditional hormone therapy

- So-called "bioidentical hormones" should be considered to have the same safety issues as traditional postmenopausal hormone therapy until clinical trials can specify their safety and effectiveness. (The statement refers to custom-made alternatives to FDA-approved estrogen and progestogen formulations.)

Breast cancer risk

- The risk of breast cancer probably increases with EPT use but not with ET use.

Coronary heart disease prevention

- The role of both ET and EPT in primary prevention of coronary heart disease remains unclear, especially in younger women starting therapy early and continuing for a number of years; however, until that evidence is forthcoming, ET or EPT should not be used for primary or secondary prevention of coronary heart disease.

Renewed recommendations

Hormones for hot flashes

- Strong endorsement to use ET/EPT for menopause-related symptoms such as hot flashes.

Hormone dosage

- ET or EPT should be limited to the lowest effective dose.

The complete report is in the NAMS official journal, *Menopause* (2004;11:589-600) and can be accessed at www.menopause.org

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