

Transdermal Estradiol versus LH-RH Agonists for Androgen Deprivation Therapy: Benefits and Risks

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LAY ABSTRACT

Transdermal estradiol (tE2), in the form of patches or topical gel, can provide the same level of androgen suppression (AS) for advanced prostate cancer (PCa) as Lupron and Zoladex; i.e., LH-RH agonists (aLH-RH). tE2 treatment prevents the hot flashes, weak bones, and increased risk of a fatal heart attack associated with aLH-RH. It also costs much less.

However, tE2 is not usually prescribed for AS. To better inform clinicians and patients about the tE2 option for AS, I undertook a comparative review of the pharmacology and side effects of estrogen versus aLH-RH.

tE2's major problematic side effects, not shared with aLH-RH, are breast tenderness and breast development. Various strategies exist for dealing with these. Breast cancer risk is also higher for men on tE2 than on aLH-RH. Thus, patients on long-term tE2 should be monitored for breast cancer just as women are.

Low testosterone in men has been linked to both depression and cognitive impairment (e.g., memory loss, difficulty solving spatial relationship problems). There is much variation, though, in the results from the published studies. Age and other aspects of patient health may be important factors accounting for the different results. One study has suggested that tE2 can reverse memory loss from AS, but further investigation is needed.

AS suppresses libido. Estrogens, such as estradiol, significantly increase sexual interest and activity in voluntarily orchiectomized males. This may be particularly important to both patients and their partners.

In women, elevated levels of estrogen increase the risk of urinary incontinence. This risk is uninvestigated in PCa patients on tE2, but awareness of it may inform patients indirectly about their own blood estrogen levels.

Men express concern about taking a female hormone. This may be related to their not being informed about the many roles estrogen plays in the normal male body.

Overall, patients are likely to have a higher quality of life on tE2 than on aLH-RH. However data from studies with pre- and post-menopausal women, plus information on the pharmacology of estradiol, suggest that **the benefits of tE2 over aLH-RH are all more likely to be exhibited, if tE2 is provided before the patients develop menopausal symptoms from AS.** This suggests that tE2 should be offered to patients before rather than after they have been on aLH-RH agonists for any length of time.

tE2 is usually prescribed in the form of skin patches, which are unsightly, often loosen with exposure to water, and may cause skin irritation. Gel delivery of tE2 eliminates skin irritation and leaves no marks on the skin. Gel is easy to apply and may consequently be more acceptable to patients.

INTRODUCTION

The key treatment for advanced androgen-dependent prostate cancer (PCa) is androgen suppression (AS) achieved via surgical or chemical castration. Although LH-RH agonists (aLH-RH) are most commonly used for chemical castration, **parenteral estrogens can provide the same level of AS at a much lower cost** [1,2]. Currently, transdermal estradiol (tE2) is rarely used as the primary mode of hormonal therapy in the treatment of PCa.

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The benefits and risks of tE2 versus aLH-RH are reviewed here to explore offering tE2 as a monotherapeutic alternative to aLH-RH for advanced PCa.

METHODS

Data were taken from standard data bases (e.g., PubMed, Google Scholar), augmented with personal information provided by patients.

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SIDE EFFECTS

Hot flashes—

- aLH-RH cause hot flashes in 50-75% of PCa patients [3].

tE2 prevents hotflashes in androgen-suppressed males [2,4-6].

Osteoporosis and bone fractures—

- Both increase significantly with aLH-RH [7-12]. Bisphosphonates are commonly prescribed to maintain bone integrity for patients on long term aLH-RH [13,6],

but...

- They increase risk of both renal dysfunction and osteonecrosis [14-16].

In contrast, tE2 improves bone density when used as monotherapy to treat PCa [7] and does not increase the risk of osteonecrosis.

Metabolic syndrome, lipid profile and cardiovascular risk—

- Low circulating testosterone is associated with metabolic syndrome in men [17].
- aLH-RH treatment heightens the risk of incident diabetes, coronary heart disease, myocardial infarction, and sudden cardiac death in PCa patients [18,19].
- Thromboembolic risk is high with oral estrogens but is circumvented with tE2 [3,5,20-22].
- Estrogen is cardioprotective in both men and women (if initiated before menopause, for women) [23].
- Cardiovascular benefit is therefore likely to be manifested in those PCa patients who begin tE2 therapy **before** taking an aLH-RH, based on identical biochemical pathways in women and men [21,23-25].
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Sexual interest and performance; impact on relationships—

- aLH-RH treatment diminishes both sexual potency and sexual interest (e.g., [13,6,26] and many other studies).
- This, and other PCa treatments that diminish sexual functioning and libido, impact the quality of life of patients **and** partners [1,3,28-38]; reviewed in [39].
- One recent (small) study suggests that ~50% of patients on aLH-RH experience a stressful decline in spousal relations [40].
- Unclear whether estradiol therapy does [41] or does not [42] improve sexual functioning in menopausal women.

However...

Indirect evidence suggests that estrogen increases libido in androgen-suppressed PCa patients.

For example,

- PCa patients on the anti-androgen bicalutamide report less loss of sexual interest and potency than those on aLH-RH [43]; see also [44-46].

Recent data show that exogenous estrogen significantly ($p < 0.001$) increases both self-reported sexual interest and sexual activity in orchiectomized males [47].

Hot flashes—

- aLH-RH cause hot flashes in 50-75% of PCa patients [3].

tE2 prevents hot flashes in androgen-suppressed males [4-6,2].

Cognition—

- Androgen suppression appears to cause some cognitive impairment in both males and females [48-52],

However...

- The nature of the cognitive loss from aLH-RH drugs remains controversial (e.g., [53-58]).
- Women, who underwent an oophorectomy before menopause had increased risk of cognitive impairment [59], yet women in early menopause failed to show cognitive improvement with a hormone replacement therapy (HRT) that was both estrogenic and progesteric [41].

Taxel et al. [56] failed to find a cognitive benefit to estradiol administered to older patients on AS. In contrast, Beer et al. [60] reported that tE2 can reverse the neurotoxic effects on memory caused by aLH-RH.

- Sample sizes in all these studies were small and the age, comorbidities, and length of time the patients were on AS may account for some, if not all, of the difference.

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Sherwin [61,62] proposed for women a “critical period hypothesis which holds that ET [estrogen therapy] will effectively protect against memory decline when it is initiated around the time of menopause, but not when considerable time has elapsed since the menopause” (see also [63]). By extension, tE2 is likely to be most effective in protecting cognitive abilities in PCa patients, if started before they go on any aLH-RH drugs [64].

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Depression—

- Increased in both menopausal women and androgen-suppressed men [65].

Whether increased depression is directly and singularly due to hormonal status is controversial for both women [66] and men [67]. Age and comorbidity may be more significant factors for PCa patients.

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The effect of tE2 monotherapy versus aLH-RH monotherapy on depression in PCa patients has not been investigated.

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Breast cancer risk—

- Increased in PCa patients on parenteral estrogen [68].
- Patients on tE2 should be monitored for breast cancer.

When both the risk of breast cancer and distress about gynecomastia are high (see below), patients on tE2 might be best served by subcutaneous mastectomy.

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Gynecomastia—

- How men react to gynecomastia is highly variable and ranges from finding it desirable, as an autoerotic paraphilia [69,70], to shameful and stigmatizing [40,37,71].
- Occurs in few (<15 %) patients on aLH-RH,
- Common (>70%) for patients on estrogenic compounds [72].
- Particularly bothersome when accompanied by increased nipple sensitivity and mastalgia.
- Can be partially prevented with prophylactic external irradiation [73,74,75,76], but this may not significantly reduce breast pain for PCa patients on tE2 monotherapy [5].
- Increased long term risk of breast or lung cancer in PCa patients on tE2 treated with prophylactic radiation is uninvestigated [72].

Selective estrogen-receptor modulators, such as tamoxifen, have been recommended as a treatment for gynecomastia in PCa patients taking anti-androgens [74,75,76,72]. **Although gynecomastia can be significantly reduced with tamoxifen, this drug treatment is likely to undermine the sexual and cognitive benefits of estrogen** (cf. [77,78]). Alternatively, mastectomy, as a *post facto* option for gynecomastia, is gaining acceptance [79]. This option alleviates the breast cancer risk without diminishing estrogenic benefits.

Incontinence—

- No increase in urinary incontinence reported for PCa patients on aLH-RH.
- Although uninvestigated for PCa patients treated with tE2, increased incidence reported by postmenopausal women on estrogen therapy [80,81].
Therefore...
- Physicians should be aware that incontinence may increase in PCa patients on tE2. [Anecdotally, patients may be able to use stress incontinence to self-assess the concentration of estrogen in their serum.]

OTHER CONSIDERATIONS

Delivery options—

- Variable dose tE2 patches (e.g., Climara®, Estraderm®, Vivelle-Dot®) allow menopausal women on HRT to reach their target dose wearing a single patch.

However...

- PCa patients report using up to 12 patches at a time in order to achieve adequate AS.
- Patches can cause irritation, absorb dye from clothing (making them unsightly) and adhesion is often reduced from sweating/showering/swimming.
- Topical gel (e.g., Estrogel®) is a potentially better, simpler delivery vehicle.
- Gel is easily applied; leaves no marks on the skin; does not cause irritation; dries quickly. May be more tolerable and easier for patients than multiple patches.
- Recent clinical trials of tE2 for PCa have used patches only; the gel should be considered as an alternative.

Patient acceptance of estrogen therapy—

- Patients may express concern that a “female” hormone will be more emasculating than aLH-RH.
- Acceptance of tE2 as an alternative to aLH-RH may be enhanced if patients are informed of the many roles estrogen plays in the normal male body [63,45,46].

SUMMARY

tE2 is currently offered to some androgen-suppressed PCa patients to control hot flashes from aLH-RH. Excluding gynecomastia and the slight increased risk of breast cancer, **tE2 appears to provide overall better quality of life than aLH-RH.**

Following data from women, who experienced estrogen deprivation before menopause (e.g., from oophorectomy) plus those who began HRT at versus post-menopause, the positive aspects of estrogen therapy are likely to be most readily demonstrated, **if initiated at the time of menopause and not later. By extension, the positive osteological, cardiovascular, cognitive, and sexual benefits of tE2 are all more likely to be seen in PCa patients, if used as primary rather than secondary hormonal therapy; i.e., before rather than after patients have started on an aLH-RH.**

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Note: References numbered 10, 75 and 76 are duplicated in the list above due to a collating error when the references were converted to a numbered list. The correct reference for each duplicated number should be obvious from the context in the poster and the title of the papers.

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