Estradiol for the mitigation of adverse effects of androgen deprivation therapy

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Abstract

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men. Conventional endocrine treatment for PCa leads to global sex steroid deprivation. The ensuing severe hypogonadism is associated with well-documented adverse effects. Recently, it has become apparent that many of the biological actions attributed to androgens in men are in fact not direct, but mediated by estradiol. Available evidence supports a primary role for estradiol in vasomotor stability, skeletal maturation and maintenance, and prevention of fat accumulation. Hence there has been interest in revisiting estradiol as a treatment for PCa. Potential roles for estradiol could be in lieu of conventional androgen deprivation therapy or as low-dose add-back treatment while continuing androgen deprivation therapy. These strategies may limit some of the side effects associated with conventional androgen deprivation therapy. However, although available data are reassuring, the potential for cardiovascular risk and pro-carcinogenic effects on PCa via estrogen receptor signalling must be considered.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, after lung cancer. Worldwide it is responsible for 7% of all deaths in men, making it the fifth leading cause of male cancer death (globocan.iarc.fr). There is high inter-country variability in prevalence, with less variation in attributable mortality (Bourke et al. 2013), due to differences in rates of prostate-specific antigen testing, with typically higher rates in more developed countries.

Androgen deprivation therapy (ADT) has been a cornerstone of PCa management since the 1940s. A variety of approaches have been used: bilateral orchiectomy; high-dose oral or parenteral estrogens; luteinizing hormone-releasing hormone (LHRH) agonists (LHRHa); LHRH antagonists; androgen receptor (AR) antagonists, and extragonadal androgen synthesis inhibitors. LHRHa are the main form of ADT in current use and nearly 50% of men with PCa can expect to undergo this treatment (Bourke et al. 2013).

With improving survival rates for PCa, and the recognition that most men with PCa do not die from it (Lu-Yao et al. 2004), there has been considerable focus on the metabolic side effects of long-term LHRHa. Men receiving this treatment experience constitutional symptoms and vasomotor symptoms (VMS), bone structural deterioration and fractures, a tendency to sarcopaenic obesity and insulin resistance, and subtle cognitive and mood changes (Grossmann & Zajac 2011).

LHRHa cause global sex steroid deprivation, with near-undetectable levels of both androgens and estrogens...
within 30 days of administration (Sharifi et al. 1996). A growing body of basic scientific and clinical studies has now clearly demonstrated that many of the biological actions of testosterone in men are mediated by its metabolite, 17β-estradiol (E2). Loss of E2 signalling appears to be primarily responsible for certain components of the male hypogonadal syndrome such as vasomotor instability, bone deterioration and fat gain (Finkelstein et al. 2013, 2016, Taylor et al. 2016).

This review will discuss the role of estrogens in the endocrine treatment of PCa. While estrogens have been used extensively in the past as a mode of ADT, they have been replaced in current practice with LHRHa because the latter have been considered a safer and better tolerated alternative. Advances in the understanding of the biological importance of E2 in men have prompted a recent resurgence of interest in using E2 in men with PCa either as an alternative to LHRHa, or as low-dose replacement therapy in addition to LHRHa. Widespread clinical adoption of such strategies will require convincing evidence that estrogens can be used without the adverse cardiovascular impact of earlier regimens, and that such use will not have pro-carcinogenic effects.

The material presented is based on peer-reviewed journals indexed on the PubMed database from 1940 to May 24, 2017, using the following search terms: prostate cancer, androgen deprivation therapy, hypogonadism and estradiol. Studies were limited to those published in English and studies in men. In addition, pertinent review articles were searched for additional publications, and relevant articles were selected.

**Past and present endocrine treatments for prostate cancer**

In 1941, Huggins and Hodges published evidence that orchiectomy or injection of estrogens (stilbestrol or ethinyl estradiol benzoate) caused regression of metastatic PCa in men, while testosterone injections promoted growth (Huggins & Hodges 1941, Huggins 1967). On the strength of this work, and a large retrospective observational study that reported better survival in men receiving endocrine treatment (Nesbit & Baum 1950), orchiectomy and oral diethylstilbestrol (DES) became standard treatments for PCa. Orchiectomy works by surgical removal of the predominant source of testosterone production, while DES exerts ER-mediated negative feedback on pituitary gonadotrophs, resulting in hypogonadotropic hypogonadism. Estrogens also directly inhibit testicular testosterone production (Melner & Abney 1980) associated with morphological changes in Leydig cells (Leavy et al. 2017). DES has additional pharmacologic anti-cancer effects such as antagonism of androgen-induced telomerase activity in PCa cell lines (Geier et al. 2010).

A series of retrospective randomized controlled trials (RCTs) were performed by the Veterans Administration Cooperative Urological Research Group (VACURG) in the 1960s (Byar 1973). These trials compared various doses of DES (0.2–5 mg) with placebo in localized PCa after radical prostatectomy, and in metastatic disease. The VACURG studies demonstrated efficacy of DES on PCa outcomes at the expense of increased cardiovascular morbidity and mortality at higher doses. This helped to define a role for oral DES (1–3 mg) in symptomatic locally advanced or metastatic disease (Torti 1984).

The dose-dependent elevation in cardiovascular mortality caused by oral estrogen was due to an increase in myocardial infarction, stroke, ischaemic cardiomyopathy and pulmonary embolism (Byar 1973). This effect was shown to be associated with elevations in blood pressure and adverse alterations in hepatic metabolism of clotting factors, lipids and other proteins (Schoultz et al. 1989). As will be discussed in the ‘Potential adverse effects of estrogen therapy’ section, these problems might be largely avoided with parenteral administration of non-synthetic estrogens.

LHRH was discovered in the early 1970s (Schally et al. 1971) and in the context of safety concerns about estrogens, leuprolide (Leuprolide Study Group 1984) and subsequently other depot LHRHAs (Seidenfeld et al. 2000) were shown to be non-inferior to orchiectomy or DES in men with metastatic PCa with respect to PCa outcomes. In comparison to high-dose synthetic oral estrogens, LHRHAs had the advantage of relative cardiovascular safety and less gynaecomastia, at the significant cost of more VMS and osteoporosis (Leuprolide Study Group 1984, Ockrim et al. 2006, Hedlund et al. 2008). These side effects ensured that interest in estrogen as an alternative continued.

Large RCTs of intramuscular polyestradiol phosphate (PEP), with median follow-up period of over 10 years, showed no overall mortality or cancer-specific survival difference compared with combined androgen blockade (CAB) (Hedlund et al. 2008) or orchiectomy (Mikkola et al. 2007). However, both the SPCG-5 trial (Hedlund et al. 2008) and the Finnprostate 6 study (Mikkola et al. 2007) demonstrated more cardiovascular morbidity in the PEP arm, without excess cardiovascular mortality in patients with metastatic disease. However, in the Finnprostate 6 study, patients with locally advanced disease did experience a higher risk of cardiovascular death (RR 3.52;
95% CI 1.65–7.54; *P* = 0.001) (Mikkola et al. 2007). The Prostate Adenocarcinoma TransCutaneous Hormones (PATCH) trial was a phase II single- investigator only- blinded RCT designed to assess safety and efficacy of high-dose transdermal E₂ vs LHRHAs in men with locally advanced or metastatic ADT (Langley et al. 2013). PATCH was reassuring with respect to cardiovascular safety, and a phase 3 study has commenced.

Most commonly used ADT modalities in current practice are LHRHAs, LHRH antagonists, and much less frequently in developed countries, orchiectomy. ADT has an established role as first-line therapy in metastatic PCAs where it provides symptomatic benefit (Pagliarulo et al. 2012). ADT in various durations (commonly 6 months to 3 years) is combined with definitive radiotherapy for localized intermediate- and high-risk disease and for locally advanced disease. In these settings, ADT has been shown to improve survival rate (Cornford et al. 2017, Mottet et al. 2017). ADT is also used in the adjuvant or salvage setting for biochemical recurrence following radical prostatectomy (with or without radiotherapy) although no survival advantage has been demonstrated in this context (Pagliarulo et al. 2012, Cornford et al. 2017, Mottet et al. 2017). For metastatic PCAs, ADT is generally prescribed indefinitely, although intermittent therapy may be used.

Traditional androgens such as bicalutamide are not as effective as LHRHAs as monotherapy, and their addition to LHRHAs as CAB has not demonstrated a consistent survival benefit (Seidenfeld et al. 2000). However, more effective AR blockers such as enzalutamide have survival benefits in castrate-resistant prostate cancer (CRPC), providing clinical proof of principle that CRPC remains androgen-dependent (Scher et al. 2012, Beer et al. 2014). This is also evidenced by the survival benefit reported with abiraterone, a CYP17 inhibitor which inhibits adrenal and intra-tumoural androgen synthesis in LHRHa-treated patients (de Bono et al. 2011, Ryan et al. 2013).

**Side effects of androgen deprivation therapy**

Side effects of non-estrogen modes of ADT have been reviewed (Sharifi et al. 2005, Grossmann & Zajac 2011, Collins & Basaria 2012, Cheung et al. 2014) and will only be briefly outlined. There is a justified focus on such side effects, particularly because prolonged survival is expected in most men in whom this therapy is used. Overall, PCAs have a low case fatality rate, and most men diagnosed with PCAs will die of another condition (Lu-Yao et al. 2004, Albertsen et al. 2011). Cardiovascular disorders are responsible for at least a quarter of deaths in men with PCAs (Lu-Yao et al. 2004). For localized (T1c or T2), moderately and poorly differentiated PCAs managed conservatively, PCAspecific 10-year survival is 73–98% (Albertsen et al. 2011). For men treated with adjuvant ADT following radical prostatectomy for high-risk localized disease, 5-year overall survival rate is over 95% (Dorff et al. 2011). For men who have developed CRPC, median survival was 2–3 years, even prior to widespread use of novel antiandrogens which have been shown to prolong survival (de Bono et al. 2011, Scher et al. 2012).

**Constitutional, vasomotor and sexual symptoms**

LHRHAs are associated with fatigue, anaemia, loss of libido, VMS and possibly detrimental effects on mood and cognition (Grossmann & Zajac 2011). Fatigue is likely to be multifactorial. Androgen ablation produces a mild normocytic anaemia, with haemoglobin and haematocrit within the female normal range (Grossmann & Zajac 2012). Hot flushes are experienced by approximately 70–80% of men undergoing non-estrogen-based ADT (Karling et al. 1994, Sharifi et al. 2005). They are often mild and abate, but may persist and be severe enough to warrant pharmacotherapy (Karling et al. 1994, Sharifi et al. 2005, Jones et al. 2012). Hot flushes may interfere with sleep and, along with other side effects of ADT, reduce quality of life (Cheung et al. 2016). Men undergoing ADT generally experience loss of libido, erectile dysfunction and reduced sexual activity (Grossmann & Zajac 2011). Men frequently report an associated perceived loss of masculinity and reduced relational intimacy (Donovan et al. 2015).

**Bone loss**

LHRHAs or orchiectomy lead to accelerated bone turnover and rapid bone density decline, microarchitectural deterioration, and increased fracture risk. In the first year of ADT there is an increase in bone turnover and a 5–10-fold increase in the rate of areal BMD loss (Greenspan et al. 2005). Areal BMD measured by dual-energy X-ray absorptiometry (DXA) underestimates the degree of cortical BMD loss and microarchitectural deterioration in cortical and trabecular compartments (Hamilton et al. 2010). There is a lack of prospective studies reporting fracture rates in men undergoing ADT (Diamond et al. 2004). Large retrospective studies report higher fracture rates in these men (Shahinian et al. 2005, Shao et al. 2013) and fracture post ADT was associated with a 10% 12-month mortality (Shao et al. 2013). Increased fracture risk is likely to reflect the BMD decrement, deterioration in...
microarchitecture and declines in muscle function possibly contributing to falls (Cheung et al. 2017).

**Sarcopaenia, obesity and physical function**

Men commencing LHRHa lose lean body mass and gain fat mass. Total body fat mass increases by about 10% during the first year (Smith et al. 2002a, Greenspan et al. 2005, Spry et al. 2013) but whether visceral fat mass increases remains controversial (Grossmann et al. 2013). Lean body mass decreases during the first year of ADT. However, the lack of adequate controls in many longitudinal studies makes it difficult to distinguish the magnitude of the ADT effect from that of ageing alone or cancer itself (Cheung et al. 2014). In one appropriately controlled study, there was a significant 12-month lean body mass decline of 3.5±0.5% in men newly commencing non-estrogen ADT (Greenspan et al. 2005). Effects occur early and appear to plateau after 6 months of ADT. In the lower limb, LHRHa therapy may cause selective decrements in quadriceps, soleus and iliopsoas function and was associated with emergent gait broadening and decline in gait speed at 12 months (Cheung et al. 2017) but whether ADT itself causes falls has not been rigorously studied.

**Insulin resistance, dyslipidaemia and cardiovascular risk**

Causal links between sarcopenia and metabolic alterations that enhance cardiovascular risk have been uncovered in recent years (Basaria & Bhasin 2012, Boström et al. 2012, Guridi et al. 2015). It is likely that ADT-induced sarcopenic obesity is responsible for the increase in insulin resistance observed with ADT (Smith et al. 2006), but there may be body composition-independent effects of sex steroid deficiency, either directly mediated by low testosterone, and/or because of low E$_2$ (Grossmann et al. 2013). ADT is also associated with increased triglycerides, increased total cholesterol, and reductions in high-density lipoprotein (HDL)-cholesterol (Grossmann & Zajac 2011). In some large observational studies, there is an increase in the incidence of diabetes and of cardiovascular events in men undergoing ADT, but there are contradictory conclusions in other studies, and causal relationships have not been established (Collins & Basaria 2012).

**Mood and cognition**

Evidence for the cognitive effects of ADT is limited. AR and ER are abundant in the prefrontal cortex, amygdala and hippocampus (Beer et al. 2006). Animal studies indicate important roles for testosterone and E$_2$ in memory and learning but human studies have generally been small and have reached mixed conclusions. Studies in men undergoing ADT have also reported contradictory results (Donovan et al. 2015). A systematic review of small observational controlled studies concluded that ADT appears to have subtle negative effects on specific limited cognitive domains such as visuospatial abilities and executive functioning (Nelson et al. 2008). An ADT-related decline in visuomotor task performance is also supported by a subsequent meta-analysis of 14 studies enrolling a total of 417 patients treated with ADT (McGinty et al. 2014). The included studies compared cognitive test performance with healthy controls, men with PCa not undergoing ADT, or individual pre-ADT baselines. Although available evidence does not suggest that ADT causes global cognitive dysfunction, the small sample sizes in studies to date preclude exclusion of negative effects of ADT in other cognitive domains (Donovan et al. 2015). These impacts need to be confirmed in larger longitudinal controlled studies that attempt to adjust for the influence of other side effects of ADT that may affect cognition, for example, effects on mood and fatigue.

Observational studies report a high prevalence of depressive symptoms in men receiving ADT, but this may be due to effects of age, PCa, and comorbidities (Shahinian et al. 2006). In an analysis of over 78,000 men with non-metastatic PCa and without prevalent depression in the SEER database, those who received ADT within 6 months of diagnosis had a 23% increased risk of incident depression over the following 2.5 years, adjusting for a range of demographic and clinical variables (Dinh et al. 2016). Risk of depression increased with duration of ADT. Although the potential for unrecognized confounding remains, it seems likely that ADT causes more cases of depression. Whether this is a direct effect of medical castration or a result of other physical effects of ADT is unclear (Donovan et al. 2015).

**Some major side effects of ADT may be mitigated by estradiol**

Accumulating evidence suggests that in men, many of the biological actions of testosterone are not direct, but are mediated by E$_2$. It follows that side effects of non-estrogen ADT on bone and body composition, vasomotor stability, and brain may be mediated by E$_2$ and not testosterone deprivation. Discerning E$_2$-specific actions in men has...
been challenging, partly because of assumptions that sequelae of hypogonadism are due to androgen deficiency (Khosla et al. 2001, Finkelstein et al. 2013). Furthermore, 50–75% of circulating E2 in men is derived from extragonadal aromatization of androgens (Longcope et al. 1969, Kelch et al. 1972, MacDonald et al. 1979), meaning that in normal, untreated hypogonadal, and testosterone-treated hypogonadal men, testosterone and E2 concentrations are highly correlated (Lakshman et al. 2010). This has made the individual contributions of testosterone and E2 to male physiology difficult to discern.

E2 acts as a hormone, circulating in blood to act at distant sites, but is also locally produced by aromatase in fat, bone, brain and other tissues (Sasano et al. 1997, Biegon et al. 2010) to act in an autocrine or paracrine fashion. E2 is the most potent natural agonist at estrogen receptors alpha (ERα) and beta (ERβ). ERα and ERβ are predominantly located in the nucleus where they function as ligand-dependent transcription factors. Membrane-associated forms are responsible for activation of non-genomic pathways (Razandi et al. 2004). Further E2 actions are mediated by the G-protein-coupled estrogen receptor 1 (GPER; previously GPR30). E2-mediated activation of GPER leads to activation of cytoplasmic second messenger pathways (Revankar et al. 2005). GPER and membrane-ER activation are mechanisms by which E2 exerts rapid cellular signalling effects and also indirectly modifies transcription of genes that do not contain traditional estrogen response elements (Björnström & Sjöberg 2005).

Evidence to support an important role of E2 deficiency in the pathophysiology of hypogonadism in men has come from five main lines of enquiry: (1) reports of rare cases of individuals with congenital aromatase, AR or ER deficiency; (2) basic investigations of androgen and estrogen action, for example, murine models; (3) cross-sectional and longitudinal population-based observational studies of the associations between sex hormones and various surrogate or clinical endpoints; (4) studies of the use of estrogens for ADT; and (5) experiments in healthy men, in which short-term hypogonadism is induced medically, combined with aromatase inhibition and differential add-back of sex hormones, to isolate parts of the hypogonadal syndrome that are T-dependent, E2-dependent or both. Taken together, these lines of evidence support a primary role for E2 in vasomotor stability, skeletal maturation and maintenance, and prevention of fat accumulation (Table 1).

### Table 1 Hypotheses for E2 add-back in men undergoing non-estrogen ADT.

<table>
<thead>
<tr>
<th>Clinical side effect</th>
<th>LHRHa (low testosterone/low E2)</th>
<th>LHRHa+E2 add-back (low testosterone/normal E2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>No benefit</td>
<td>Improved</td>
</tr>
<tr>
<td>Bone density and</td>
<td></td>
<td>Improved</td>
</tr>
<tr>
<td>microarchitectural</td>
<td></td>
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<tr>
<td>deterioration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat gain</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Muscle loss</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Vasomotor symptoms</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Sexual symptoms</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>Cognitive and mood</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>decline</td>
<td></td>
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</tr>
</tbody>
</table>

E2, estradiol; LHRHa, luteinizing hormone-releasing hormone agonist.

### Effect of estradiol on vasomotor symptoms

VMS, predominantly hot flushes and night sweats, are experienced by 70–80% of women during the perimenopause (Jayasena et al. 2015) and a similar proportion of men undergoing ADT (Karling et al. 1994, Sharifi et al. 2005). Rapid estrogen withdrawal appears to mediate flushes in women via an increase in release of neurokinin B, and possibly other mediators, from the hypothalamus (Jayasena et al. 2015). Neurokinin B acts on neurokinin 3 receptors in the hypothalamic median preoptic nucleus, to stimulate heat dissipation effectors such as cutaneous vasodilatation, diaphoresis and cold-seeking behaviour (Rance et al. 2013, Jayasena et al. 2015). In perimenopausal and postmenopausal women, estrogen replacement is the most effective pharmaceutical strategy for mitigating hot flushes (Nelson 2004), although an oral neurokinin 3 receptor antagonist recently appears promising (Prague et al. 2017). Topical E2 is effective at applied doses as low as 12.5–25µg daily (Gadomska et al. 2002, Shulman et al. 2002, Simon et al. 2007). However, in hypogonadal men, including those undergoing ADT, the relative roles of androgen and estrogen deficiency to the pathophysiology of hot flushes have only been recently explored.

Finkelstein and coworkers developed an elegant experimental paradigm to distinguish the roles of testosterone deficiency from those of E2 deficiency in the pathogenesis of a range of hypogonadal symptoms and sequelae (Finkelstein et al. 2013). For 16 weeks, LHRHAs were administered to a cohort of healthy male volunteers to produce castrate levels of testosterone and E2 before...
add-back of one of four doses of testosterone gel or placebo, so that serum testosterone concentrations ranged from castrate to slightly supraphysiologic. A control cohort received placebo LHRHa and placebo testosterone gel. A second cohort of men were additionally given an aromatase inhibitor (AI) to clamp E$_2$ at very low levels, independent of testosterone add-back. This design allows isolation of the effect of testosterone to determine physiological effects that are directly testosterone mediated and those that require aromatization of testosterone to E$_2$. It also allows calculation of thresholds for certain effects. The experimental design does not provide for direct observation of the effects of graded E$_2$ add-back in the absence of T. These effects were inferred by directly comparing outcomes between groups receiving the same dose of testosterone replacement, with or without AI, and by linear regression modelling. In these studies, testosterone was measured by immunoassay and E$_2$ by mass spectroscopy.

Using this experimental paradigm, E$_2$ deficiency was shown to be the primary stimulus for VMS in men, although testosterone did have some mitigating effect at high levels (Taylor et al. 2016). Overall, men who received AI had more VMS than men who did not. Men with low E$_2$ levels (<10 pg/mL; 37 pmol/L) experienced more VMS than controls even when serum testosterone levels were supraphysiologic. In men receiving AI, after adjusting for small differences in E$_2$ levels between testosterone gel dose groups, testosterone replacement did not significantly reduce the incidence of VMS compared with placebo gel until a supraphysiologic replacement dose of 10 g/day. The authors concluded that physiologic levels of androgens do not play a major role in the regulation of VMS.

Clinical studies comparing estrogen to other forms of ADT have shown that men treated with estrogen are less troubled by hot flashes (Spetz et al. 2001, Hedlund et al. 2008, Langley et al. 2013). In SPCG-5, 70% of men receiving PEP were free of hot flashes compared to 26% of men receiving CAB. Similarly, in PATCH, 75% of men receiving E$_2$ and 44% of men receiving LHRHa were free of hot flashes at 6 months follow-up (Langley et al. 2013). Therefore, with the caveat that none of these studies included a placebo group to account for hot flash prevalence in eugonadal men, avoiding a hypoestrogenic state does not appear to be totally effective in preventing hot flashes.

In the treatment of VMS, small uncontrolled studies of low-dose oral DES (Miller & Ahmann 1992, Smith 1994) and transdermal E$_2$ patches (Gerber et al. 2000) suggest estrogens might be effective in treating hot flashes in men receiving other, non-estrogen-based forms of ADT. In a double-blind placebo-controlled crossover trial, 1 mg DES was effective in reducing hot flush severity in 14 men after orchiectomy (Atala et al. 1992).

Effect of estriadiol on sexual symptoms

Animal studies suggest an important role for estradiol in male sexual behaviour (Davidson 1969, Ogawa et al. 2000, Wibowo et al. 2011). However, case reports of men with congenital aromatase deficiency have generally reported normal sexual function, and whether there is improvement with estrogen replacement is controversial (Jones et al. 2007). In the context of PCa, better maintenance of sexual function has been suggested in men receiving ADT that is estrogen based (Wibowo et al. 2011), but there have been no prospective randomized trials and firm conclusions cannot be drawn.

In Finkelstein’s experiments, changes in libido and erectile function were related to changes in both testosterone and E$_2$ (Finkelstein et al. 2013). However, anastrozole penetrates the blood–brain barrier poorly because it is a substrate for P glycoprotein-mediated efflux mechanisms (Miyajima et al. 2013). Therefore, brain aromatase inhibition by this agent is expected to be low and Finkelstein’s cohort of men with systemic low, normal or high testosterone and low E$_2$ may not have had corresponding low brain E$_2$ levels. Therefore, local, brain-produced T- and E$_2$-specific physiological effects on measures such as libido, and perhaps erectile function, on which cognitive processes have an impact, are not well characterized. It remains unproven whether E$_2$ would be effective in mitigating these sexual side effects of non-estrogen ADT.

Effect of estradiol on bone

The reduction in bone density associated with male hypogonadism appears to be mediated by deficiency of both testosterone and E$_2$, although E$_2$ deficiency appears to be most important. Testosterone effects may be partly indirect, through anabolic effects on muscle mass, which increases bone mass by increasing mechanical load. Untreated men and women with congenital aromatase deficiency develop eunuchoid skeletal proportions, continued linear growth and high-turnover osteoporosis (Morishima et al. 1995, Carani et al. 1997,
Hermann et al. 2002). A similar skeletal phenotype was described in a man with a homozygous ERα mutation (Smith et al. 1994). In the cases of aromatase deficiency, but not in the case of ERα deficiency, estrogen treatment reduced bone turnover, fused epiphyses and improved bone density. In a cross-sectional study, women with complete androgen insensitivity syndrome (XY karyotype) had moderate deficits in lumbar spine BMD that was more marked in those with poor adherence to estrogen therapy (Marcus et al. 2000). There was no deficit in areal BMD in women with partial androgen insensitivity suggesting some beneficial effects on BMD of residual androgen responsiveness in bone or muscle. While instructive, the phenotype of patients with deficiency of sex steroid action during fetal, childhood and pubertal growth and development may not accurately represent the pathophysiology of bone disease that occurs during adult onset hypogonadism (Khosla et al. 2001, Finkelstein et al. 2016).

Cross-sectional and longitudinal observational studies of associations between areal BMD and sex steroid levels in older men have shown stronger associations with E2 than with T, although associations are generally weak (Khosla et al. 2001). The association between serum sex steroid levels and bone microarchitectural parameters was examined in 440 elderly Swedish men (Vandenput et al. 2001). Serum E2, measured by mass spectrometry, was inversely associated with cortical porosity. The importance of E2 action on bone is supported by a genome-wide association study showing a common ERα polymorphism is associated with reduced cortical volumetric BMD (Paternoster et al. 2013), and also by interventional studies.

Nine weeks of AI treatment in 15 healthy older men increased T, modestly reduced E2 and reversibly increased bone remodelling as measured by serum C-terminal telopeptide of type I collagen (CTX) (Taxel et al. 2001). In a 12-month RCT of AI treatment in 69 older men with low testosterone levels, spine BMD slightly but significantly declined in the AI group without significant changes in bone remodelling markers (Burnett-Bowie et al. 2009). The AI raised testosterone levels into the eugonadal range for young men but, as with other studies of AI in men without gonadotropin suppression, E2 only modestly declined and remained within the normal range (Burnett-Bowie et al. 2009). In a 6-week study of 59 healthy elderly men, LHRHAs were combined with AI plus topical testosterone add-back, topical E2 add-back, both or neither (Falahati-Nini et al. 2000). Bone remodelling as measured by urinary total deoxypyridinoline and N-terminal of type 1 collagen increased in groups without E2 add-back, but there was no statistically independent effect of testosterone. Serum N-terminal propeptide of type 1 collagen (P1NP) fell in groups without E2 add-back, with no independent effect of testosterone, suggesting an E2-dependent reduction in collagen synthesis by all cells of osteoblast lineage (Khosla et al. 2001). Osteocalcin similarly fell in groups with no testosterone or E2 add-back, suggested to reflect apoptosis of mature osteoblasts, but this was prevented by either testosterone or E2 add-back, or both. Short-term studies of bone remodelling markers do not allow conclusions to be made regarding net bone resorption or bone formation (Seeman & Martin 2015).

Finkelstein and coworkers applied their experimental paradigm to biochemical markers of bone turnover and BMD to isolate the individual effects of testosterone and E2 deficiency on the high-turnover bone loss that occurs in hypogonadism (Finkelstein et al. 2016). Serum CTX and P1NP were measured. Areal BMD was measured using DXA and spine trabecular BMD by quantitative computed tomography. Elevations in bone turnover markers, measured as a percentage of baseline, tended to be higher in men who received AI compared to those that did not, but in this short-term study, these changes were only significant for CTX. Within both cohorts, CTX elevations were also higher in those who received lower doses of testosterone replacement. Although changes in BMD were small over 16 weeks, similar patterns were seen with respect to BMD, with greater declines in men receiving AI than men who did not, and greater declines in men with lower testosterone replacement doses in both AI and no AI cohorts. Trabecular BMD at the spine declined by 4–5% in men receiving AI, and was significantly different than control at each testosterone replacement dose. A subset of men receiving AI also underwent high-resolution peripheral quantitative CT to measure bone microarchitecture at the distal radius and tibia. Volumetric BMD tended to decline from baseline in men receiving AI. Volumetric BMD and changes in indices of skeletal microarchitecture were independent of testosterone replacement dose, suggesting a predominant effect of E2 deficiency.

In the context of ADT for PCa, few studies have looked specifically at the efficacy of estrogens in preventing bone deterioration. In a nested BMD substudy of the PATCH trial, 74 men with locally advanced or metastatic PCa, randomized to ADT with LHRHa or E2 patches, underwent DXA scans at baseline, 1 year and 2 years (Langley et al. 2016). Data were available on 60 men for the primary outcome of 1-year change in lumbar spine BMD. At all
anatomical sites, at both time points, BMD increased compared with baseline in the E₂ arm and decreased in the LHRHa arm. This resulted in a 6.7% (3.7–9.7%; P < 0.001) improved BMD at the lumbar spine in the E₂ group compared with LHRHa group (mean absolute change of +0.069 g/cm³ vs −0.021 g/cm³, respectively). Fractures were not reported, but the PATCH bone substudy provides strong evidence that ADT using transdermal E₂ prevents the decline in BMD caused by LHRHa.

Skeletal events including fractures were measured as a secondary outcome in the SPCG-5 trial of intramuscular PEP compared with CAB (Hedlund et al. 2008). After median follow-up of 11.7 years (10.1–13.7), 18 skeletal events including 9 femoral neck fractures and 7 spinal cord compressions had occurred in the CAB group (n = 455) and 0 had occurred in the PEP group (n = 455) (P = 0.001). Bone density was not reported in the SPCG-5 trial.

Effect of estradiol on body composition and insulin resistance

Adverse changes in body composition are important drivers of insulin resistance leading to diabetes and elevations in cardiovascular risk. Both T-deficiency-induced muscle loss and E₂-deficiency-induced visceral fat gain may be important in this process. Muscle loss is likely to be important via dual mechanisms of loss of tissue capable of insulin-independent glucose uptake; and also loss of myokine signalling (Basaria & Bhasin 2012).

Androgens, acting on the AR, promote myogenic differentiation of mesodermal stem cells and inhibit adipogenic differentiation (Bhasin et al. 2003). Loss of these AR-mediated effects in men undergoing LHRHa therapy would not be expected to be mitigated by estrogens. However, some fat mass-reducing effects of androgens may be mediated by aromatization to estrogens. Global aromatase knockout mice have more fat mass and less muscle mass than wild type mice, and men and postmenopausal women have a different body fat distribution pattern than premenopausal women (Jones et al. 2000). Case reports of men with congenital aromatase deficiency describe excess adiposity and insulin resistance (Jones et al. 2007) and AI treatment in healthy men reduces insulin sensitivity (Gibb et al. 2016). Similarly, mice (Bryzgalova et al. 2006) and men (Smith et al. 1994) with defective ERα have insulin resistance.

While most evidence suggests that skeletal muscle is an androgen-dependent organ, a population-based cross-sectional study of 3014 elderly Swedish men, serum E₂ but not testosterone was positively associated with lean mass (Vandenput et al. 2010). Conflicting results with respect to muscle strength were obtained in a Dutch cross-sectional study (van den Beld et al. 2000). By comparison, Finkelstein reported that E₂ did not exert an effect independent of testosterone on total body lean mass, thigh muscle area or leg press strength. However, increases in percentage body fat, intra-abdominal fat area and subcutaneous fat area were primarily related to changes in E₂ levels (Finkelstein et al. 2013).

In obese young men with low-normal or frankly low free T, a 14-week placebo-controlled RCT of an LHRH antagonist with exogenous testosterone gel 10g/day combined with dutasteride (to inhibit testosterone conversion to the more potent AR agonist dihydrotestosterone, DHT), AI or placebo pill was performed to isolate the body composition effects of testosterone that were DHT- or E₂-dependent (Juang et al. 2014). A separate triple-placebo (injection/gel/pill) group acted as controls. Mean total testosterone concentration increased from group means of 9.5–13.1 nmol/L to means of 12.2 (triple placebo), 25.3 (AI pill), 38.4 (dutasteride pill) and 41.4 nmol/L (placebo pill). Post-treatment E₂ in these groups was 76.3 (triple placebo), 11.7 (AI pill), 156.5 (dutasteride pill), 203.3 pmol/L (placebo pill), as measured by immunoassay. Body composition improved (increased fat free mass percentage and decreased fat mass) with testosterone treatment of these men when it was combined with placebo or dutasteride pills but not when it was combined with AI, suggesting that these changes were E₂-dependent. Insulin sensitivity (IS), measured using euglycaemic hyperinsulinemic glucose clamp, significantly improved only in the dutasteride group, suggesting that DHT attenuates potential benefits of testosterone and E₂ on IS. However, this small (n = 57), short-term study requires confirmation.

Effect of estradiol on neurocognitive symptoms

Both E₂ and androgens have genomic and non-genomic effects in the brain that may influence cognition in men (Nelson et al. 2008). It is unknown whether subtle cognitive effects associated with testosterone deficiency, for example, on working memory, would be mitigated by E₂. There is some suggestion that certain castration effects might be due to E₂ withdrawal, such as effects on rate of learning (Nelson et al. 2008). A small 12-week RCT of testosterone supplementation with or without anastrozole in healthy eugonadal elderly men observed improvements in spatial memory in both groups compared with men receiving double placebo (Cherrier et al. 2005). Men in
the T-only group, but not men in the testosterone plus anastrozole group, had improvements in verbal memory, suggesting possible estradiol dependence of this effect (with the caveat regarding poor central nervous system penetration of anastrozole, discussed above). However, the cognitive component of the much larger testosterone trials showed that 12 months of testosterone treatment in older men with mildly low testosterone and age-associated memory impairment did not improve cognition (Resnick et al. 2017).

In the ADT context, a non-randomized pilot study investigated the effect of high-dose parenteral E2 as second-line ADT in 18 men with CRPC (Beer et al. 2006). Cognitive assessments were conducted at baseline prior to switching to E2, and 4 weeks later. A cohort of men with castrate-sensitive PCa continuing conventional ADT, and another cohort of healthy men, acted as controls. On individual repeated measures analysis verbal memory performance improved with E2 therapy and did not change in the control groups, but the interaction of group and visit was statistically insignificant in overall analysis of variance. A 9-week pilot RCT of low-dose oral E2 in 27 men receiving LHRHa demonstrated no improvements in cognitive function compared with placebo (Taxel et al. 2004). A 24-week RCT in 25 men receiving CAB administered neuropsychological tests prior to therapy, after 12 weeks of CAB and after a subsequent 12 weeks of CAB plus low-dose oral E2 or placebo (Matousek & Sherwin 2010). The hypothesized decrement in visual and spatial test scores after 12 weeks of CAB was not observed, and there was no further improvement in scores with E2 add-back.

**Estradiol is unlikely to mitigate effects of ADT that are direct sequela of testosterone deficiency**

Parts of the hypogonadal syndrome that are directly mediated by loss of AR signalling would not be expected to improve with E2 administration (Table 1). A decrement in haemoglobin is expected with ADT, often leading to a mild normocytic and normochromic anaemia. This is clearly an androgen-dependent effect. The mechanisms may involve reduced activation of AR on erythroid progenitors, unsuppression of hepcidin leading to reduced iron availability for erythropoiesis, and possibly reduced erythropoietin secretion, although data are contradictory (Grossmann & Zajac 2012).

As discussed above, relationships of sex hormones to muscle size and function remain to be fully elucidated. While observational data have shown variable associations of sex hormones with lean mass in healthy elderly men (van den Beld et al. 2000, Vandenput et al. 2010), Finkelstein’s experiments on healthy young men suggest that short-term changes in lean mass, muscle size and strength are androgen-dependent (Finkelstein et al. 2013). Decrements over 16 weeks became evident with testosterone add-back doses of 1.25 g or less corresponding to mean testosterone concentrations of 200 ng/dL (6.9 nmol/L) or less.

**Effects of estradiol on prostate cancer**

The VACURG studies found that DES in a dose of 1 mg daily, which did not reliably produce castrate testosterone levels, was no less effective on PCa than the 5 mg dose which did (Byar & Corle 1988). This finding raised the possibility that estrogens might have additional oncologic benefits. DES was shown to have direct cytotoxic effects on PCa cells in concentrations achieved in vivo by very high-dose infusions, historically used with palliative benefit in patients, although this may have been a non-ER-mediated pharmacological effect (Schulz et al. 1988, 1990, Robertson et al. 1996, Geier et al. 2010).

Subsequent epidemiologic, basic and clinical studies have demonstrated the role of estrogens in PCa to be highly complex (Di Zazzo et al. 2016, Rahman et al. 2016). The age-associated rise in PCa incidence coincides with a decrease in circulating free testosterone/E2 ratio due to declines in hypothalamic–pituitary–testicular axis function and increases in sex hormone binding globulin (SHBG) (Rahman et al. 2016, Cooke et al. 2017). However, more defined associations between E2 concentrations or testosterone/E2 ratios and PCa incidence have not been established.

Normal and neoplastic prostate tissue expresses ERα, ERβ and GPER. ERα is predominantly localized in normal and tumour stroma; ERβ is highly expressed in normal prostate epithelium and stroma but is downregulated during PCa development (Leach et al. 2016). ERα signalling promotes cell cycle progression, inflammation and carcinogenesis in the prostate, while ERβ signalling is anti-proliferative, pro-apoptotic and protective, although this may depend on the ERβ isoform (Risbridger et al. 2010, Leach et al. 2016). GPER-specific activation appears to inhibit PCa growth (Chan et al. 2010, Lau & To 2016). Prostate stromal cells contain aromatase and synthesize E2 locally from available androgens (Risbridger et al. 2007). E2 acts on local stromal and epithelial cells and there is paracrine regulation of its production, but this is lost in PCa. Increased aromatase expression in metastatic PCa lesions has been demonstrated (Miftakhova et al. 2016). Estrogens along with other non-androgen ligands may be able to activate mutated ARs as one mechanism of...
castrate resistance (Leach et al. 2016). However, clinically, AIs have been an unsuccessful strategy to treat CRPC (Smith et al. 2002b).

The net effect of estrogens or the androgen/estrogen ratio on PCA development and progression has not been established, and is unlikely to be simply defined (reviewed in Rahman et al. 2016 and Di Zazzo et al. 2016). Overall experience with the therapeutic use of estrogens in PCA does not suggest a clinically important pro-carcinogenic effect. A systematic review of 20 RCTs of the use of high-dose parenteral E$_2$ as ADT for locally advanced or metastatic PCAs found no evidence that E$_2$ treatment differed in efficacy from LHRHa or orchiectomy when comparing overall mortality (Norman et al. 2008). Oncologic outcomes from the PATCH study are yet to be reported (Langley et al. 2013).

LHRHa produce sustained suppression of LH and testosterone levels, but FSH levels tend to recover during long-term treatment (Santen et al. 1984, Bhasin et al. 1994). This FSH ‘escape’ is not seen with LHRH antagonists (Klotz et al. 2008) and appears also not to occur with ADT using high-dose estrogen therapy (Ockrim et al. 2005). Orchiectomy results in high FSH and LH levels due to the removal of negative feedback. FSH receptors are expressed in PCAs and other tumour tissues and FSH binding may have a pro-angiogenic effect (Radu et al. 2010). There has been considerable interest in the potential clinical relevance of FSH escape during ADT (Crawford et al. 2017); however, any oncological advantage of maintaining FSH suppression during ADT, including with estrogens, is yet to be proven.

**Potential adverse effects of estrogen therapy**

**Venous thromboembolism and cardiovascular risk**

Cardiovascular toxicity from oral DES comprised fluid retention, hypertension, and arterial and venous thromboembolism, manifesting as stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism (Byar 1973, de Voogt et al. 1986). Orally administered estrogens induce liver synthesis of coagulation factors, renin substrate, and many carrier proteins including SHBG (Geola et al. 1980, Schoultz et al. 1989). There are also alterations in lipoprotein metabolism with increases in triglycerides and HDL cholesterol with reduced hepatic cholesterol uptake from HDL (Schoultz et al. 1989). The adverse cardiovascular impact of early DES regimens for PCAs is likely to have been predominantly due to the prothrombotic milieu created. Orally administered estrogens for PCAs increase procoagulant factors such as Factor VII, and decrease antithrombin III, on a background of an existing hypercoagulable state (Henriksson et al. 1986, 1989). This effect is amplified for synthetic orally administered estrogens because unlike E$_2$, they are not converted to the less-potent estrone by gut-wall 17-beta hydroxysteroid dehydrogenase (Schoultz et al. 1989).

Transdermal administration of E$_2$ avoids hepatic first pass metabolism so that up to 20-fold lower doses can be administered to achieve similar serum levels (Powers et al. 1985). This means that hepatocytes are exposed to lower doses and alterations in protein synthesis and accumulation of estrone sulphate are greatly reduced (Damber et al. 1979, Powers et al. 1985, Henriksson et al. 1990). Even high doses of parenteral E$_2$ used for ADT in men with PCAs largely avoid disturbance in hepatic protein metabolism (Stege et al. 1987, Henriksson et al. 1990, Ockrim et al. 2005).

Several beneficial physiological effects of estrogen on vascular function, atherosclerosis, lipoprotein metabolism and cardiomyocyte protection are proposed (Morselli et al. 2017). In an uncontrolled study of oral E$_2$ (0.5, 1 or 2 mg daily) for 9 weeks in 22 healthy elderly men, lipid parameters improved from baseline (Giri et al. 1998). In an 8-week double-blind RCT enrolling 12 men receiving non-estrogen ADT, the effect of oral E$_2$ 1 mg daily on vascular responsiveness was compared to placebo (Komesaroff et al. 2001). E$_2$ but not placebo-treated men showed reduced vasoconstrictor responses to angiotensin II and norepinephrine, enhanced endothelial basal nitric oxide release, and reductions in systolic and diastolic blood pressure. Additionally, there are a range of proposed cellular mechanisms by which estrogens may be important for cardiomyocyte protection in the context of ageing, insulin resistance, hypertension and ischaemia (Morselli et al. 2017).

**Gynaecomastia**

Gynaecomastia reflects the ratio of AR and ER signalling in breast tissue. Reported rates following medical or surgical castration are 1–16% (Sharifi et al. 2005) but gynaecomastia is more frequent when antiandrogen monotherapy or estrogens are used. In PATCH, when it was systematically evaluated, 75% of men receiving E$_2$ experienced gynaecomastia compared with 19% receiving LHRHa (Langley et al. 2013). For symptomatic breast enlargement requiring intervention, the proportions were 9% and 0%, respectively.
Pre-treatment breast irradiation, given as a single dose, has efficacy in preventing gynaecomastia and was part of older protocols for oral DES (Beck et al. 1978) and intramuscular PEP (Norman et al. 2008). In SPCG-5, 240 mg intramuscular PEP per month over 11 years caused gynaecomastia in the majority of patients: 60% of those who received prophylactic breast irradiation and 84% of those who did not (by comparison, 48% of irradiated and 36% non-irradiated patients in the CAB group) (Hedlund et al. 2008). Severe gynaecomastia, defined as breast enlargement to a size bigger than the patient’s fist, occurred in 2% of PEP patients who received irradiation and 4% of those who did not. Three patients in the PEP group and no patients in the CAB group ceased treatment because of gynaecomastia.

**Low-dose parenteral estradiol add-back: the best solution?**

The concept of E2 add-back in men receiving LHRHa refers to the administration of E2 in doses designed to return circulating levels to normal while castrate testosterone levels are maintained. The aim of such a strategy is to reduce the incidence of ADT side effects that are due to E2 deficiency, without reducing treatment efficacy and without introducing estrogenic-side effects. However, such a strategy has not been comprehensively studied, there are no approved formulations of low-dose estrogens for men, and the dosing required to achieve physiological rather than pharmaceutical effects is uncertain.

An E2 add-back strategy would ideally avoid the use of oral and synthetic estrogens to lower risks of cardiovascular or thromboembolic adverse effects. First pass hepatic metabolism of orally administered E2 also results in higher levels of circulating estrone than E2 (Townsend et al. 1981). Transdermal E2 application results in absorption with minimal metabolism meaning that lower doses can be used, and there is a higher, more physiological, ratio of the serum E2 to estrone, and less accumulation of conjugated forms (Powers et al. 1985). This may be important in reducing the risk of gynaecomastia.

**Estradiol reference ranges and thresholds for effect**

There is some data from population-based cohorts to establish an approximate reference range for E2 in healthy elderly men. In the Health in Men Study cohort from Australia, 3690 community dwelling elderly men aged 77.0 ± 3.6 years had morning sex steroids measured by mass spectrometry (Yeap et al. 2012). This cohort excluded men with a history of androgen or antiandrogen therapy, orchiectomy or PCa. BMI was 26.5 ± 3.6 kg/m2 and 47.1% self-assessed their own health to be very good or excellent. The mean E2 concentration was 73.4 pmol/L with a reference range (2.5th–97.5th percentile) of 25.0–139.9 pmol/L. These ranges are consistent with E2 levels in 1830 elderly Swedish men taking part in the MrOS study (Vandenput et al. 2010). However, more studies are needed to more definitively establish age-adjusted reference ranges for E2, in particular among older men in whom hypogonadism has been rigorously excluded.

There are limited data on the level of serum E2 that might protect against the E2-dependent manifestations of hypogonadism in the context of castrate levels of T. In comparing blood levels of E2 and testosterone with biologic effects, it is important to recognize that E2 is produced locally from aromatase in target tissues and acts in a paracrine fashion (Simpson 2003). In healthy men and in studies of medically castrated men undergoing graded testosterone add-back, serum levels of E2 reflect the total E2 that has diffused into the blood from all tissues having been synthesized by aromatase and escaped local tissue metabolism. These blood levels, no matter how accurately measured, are an indirect reflection of total estrogen signalling which is further locally modulated by sulphoconjugation and deconjugation of estrogens (Song 2001).

As discussed, the studies of Finkelstein do not contain a cohort of men with graded E2 replacement in the absence of testosterone replacement (Finkelstein et al. 2013, 2016, Taylor et al. 2016). However, accepting that at physiologic levels testosterone is unimportant for vasomotor stability, E2 levels greater than 25 pg/mL (92 pmol/L) achieved by graded testosterone add-back were sufficient to return VMS to control levels (Taylor et al. 2016). For bone, threshold levels of 200 ng/dL (6.9 nmol/L) for testosterone and 10 pg/mL (37 pmol/L) for E2 were demonstrated, below which the risk of bone loss began to increase (Finkelstein et al. 2016) (Table 1). In the PATCH bone substudy (Langley et al. 2016), despite a 7% better lumbar spine BMD in the E2 arm compared with LHRHa arm at 12 months, there was no association between serum E2 level and BMD change at any anatomical site within the E2 arm. This could be because numbers were small, or because the achieved E2 levels were well above a threshold above which no further benefit can be obtained.

The extent to which E2 replacement in men undergoing ADT might ameliorate body composition...
effects is unknown. Lean mass, muscle mass and strength appear to be related to androgen action directly. In Finkelstein’s study, body fat accumulation appeared to be a predominantly estrogenic effect (Finkelstein et al. 2013). Men receiving AI gained body fat regardless of testosterone replacement dose. In men not receiving AI, a testosterone replacement dose of 5 g/day was sufficient to prevent fat gain, whereas men receiving 2.5 g/day did gain fat mass. Mean testosterone and E\textsubscript{2} levels in the 5 g/day group were 470 ± 201 ng/dL (16.3 ± 7.0 nmol/L) and 18.2 ± 10.2 pg/mL (67 ± 37 pmol/L), respectively. Mean testosterone and E\textsubscript{2} levels in the 2.5 g/day group were 337 ± 173 ng/dL (11.9 ± 6.0 nmol/L) and 11.9 ± 5.7 pg/mL (44 ± 21 pmol/L). An inference is that an E\textsubscript{2} level between 44 and 67 pmol/L would prevent fat gain (Table 1). But whether that applies to men with castrate testosterone levels is unknown.

Both E\textsubscript{2} and testosterone appear to be important for sexual function. In Finkelstein’s study, when testosterone levels were in the mild-moderately hypogonadal range (200–400 ng/dL; 6.9–13.9 nmol/L), greater decrements in sexual desire were seen when E\textsubscript{2} levels were <10 pg/mL (<37 pmol/L) compared to when E\textsubscript{2} levels were >10 pg/mL (>37 pmol/L) (Finkelstein et al. 2013). The effects of E\textsubscript{2} above and below 37 pmol/L in the context of castrate testosterone levels are unknown.

### Estradiol dosing to achieve physiologic levels in the context of non-estrogen ADT

There is very little data to inform dosing estimates for new studies investigating parenteral E\textsubscript{2} add-back in men undergoing non-estrogen ADT. Earlier studies of high-dose estrogen therapy do not provide useful information because the aim of this therapy was to achieve medical castration, not to achieve physiologic E\textsubscript{2} levels, and E\textsubscript{2} levels were generally not reported. When parenteral E\textsubscript{2} is used to achieve medical castration, a dose of at least 240 mg of E\textsubscript{2} per month is required (Norman et al. 2008).

In a pilot RCT of E\textsubscript{2} add-back in men receiving LHRHa, men were given 9 weeks of therapy with oral E\textsubscript{2} (1 mg/day) or placebo (Taxel et al. 2002). At baseline men had low but detectable E\textsubscript{2}, associated with castrate testosterone levels, measured by immunoassay. Oral E\textsubscript{2} recapitulated normal to high E\textsubscript{2} levels based on the reference intervals of the assay, and reduced biochemical markers of bone turnover at 9 weeks. Breast tenderness was more frequently reported in the E\textsubscript{2} arm. However, immunoassay is known to inaccurately measure low E\textsubscript{2} concentrations in men (Handelsman et al. 2014).

Other studies have added estrogens to ADT, without aiming for physiological replacement. DES 1 mg/day was added to the regimen of 14 men established on non-estrogen ADT for non-metastatic PCa (Scherr et al. 2002). Urinary collagen type I cross-linked N-telopeptides were measured and corrected for creatinine as a marker of bone turnover. Compared to a comparison group receiving 1 mg DES monotherapy, urinary N-telopeptide/creatinine was significantly higher in the ADT group. This difference was abolished by the addition of 1 mg DES to that group. However, initial allocation was non-randomized, and there was no control group of men continuing ADT without DES, and the time frame for sampling in relation to medication changes is incompletely described.

In another pilot study, 12 men with bothersome hot flushes due to LHRHa were treated with E\textsubscript{2} 50 or 100 μg/24 h patches changed twice weekly (Gerber et al. 2000). Only those receiving the higher dose had a significant increase in E\textsubscript{2} level from baseline. Mean E\textsubscript{2} in this group was 26.9 pg/mL (98.8 pmol/L) compared with 12.1 pg/mL (44 pmol/L) at baseline, measured by immunoassay. The frequency and severity of hot flashes were reduced with this dose.

#### Side effects of low-dose parenteral estradiol add-back

Whether low-dose parenteral E\textsubscript{2} add-back in men receiving LHRHa would add to side effects is unknown. Hypothesized benefits of this strategy include reduction in hot flushes, amelioration of bone density and microstructural deterioration and body fat accumulation (Table 1). It is unlikely, given the safety of high-dose parenteral E\textsubscript{2} for ADT, that low-dose E\textsubscript{2} would increase cardiovascular or thromboembolic risk, or have clinically significant pro-carcinogenic effects. Gynaecomastia would theoretically be promoted by further increasing the ER/AR signalling ratio at the breast, but whether there would be a clinically significant increase above the rate and severity associated with LHRHa alone remains to be established.

### Conclusion

Given the clinical benefits of LHRHa are mediated by testosterone deficiency, and many of the important adverse effects are mediated by E\textsubscript{2} deficiency, there is a hypothesis of benefit for trials of parenteral E\textsubscript{2} replacement in men receiving LHRHa. This is a unique clinical and ethical paradigm in which the biologic effects of E\textsubscript{2} in men in the absence of testosterone may be directly observed.


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