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Effects of Hormones and Hormone Therapy on Breast Tissue in Transgender Patients: A Concise Review

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Abstract

Purpose.—Hormone replacement therapy (HRT) has become a mainstay medical treatment option for management of gender dysphoria in transgender patients of both biologic sexes. Very little is known about the long-term effects of steroid hormone modulation on breast tissue in this population. Most of the data available on the effects of HRT on breast and reproductive tissues comes from studies of post-menopausal cisgender women. Therapeutic regimens are often provider-dependent and there are no uniform guidelines in place for cancer surveillance in transgender patients. In this review, we present what forms of hormone therapy and hormone modulation are available to transgender patients, what is known about their effects on male and female breast tissue, and what other endogenous and exogenous factors contribute to the macroscopic and cellular changes observed.

Methods.—A search of the existing literature focusing on therapeutic regimens and the effects of HRT on breast tissue provided the most current information available for this review. Recent evidence-based reports (since the year 2000) and reviews were given priority over anecdotal evidence and expert opinions when conflicting information was encountered. Older resources were considered when primary sources were needed. Given the paucity of available articles on this subject, all resources were given careful consideration.

Results.—Information about the risks associated with HRT in the current literature and in this setting is limited and often conflicting due to a scarcity of long-term studies tracking breast pathology among transgender men and women

Conclusion.—We conclude that the long-term effects of off-label pharmaceutical use for modulation of hormone levels and sexual characteristics in transgender patients have not been well studied. The tendency of steroid hormones to promote the growth of certain cancers also raises

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questions about the safety of differing doses and drug combinations. Further clinical and laboratory study is needed to better establish safety and dosing guidelines in transgender patients.

Keywords

Hormone therapy; transgender; gender-affirming hormone therapy; breast pathology; transgender breast

1. INTRODUCTION

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), *gender dysphoria* is defined as an incongruence of one's sexual identity with the gender assigned at birth. Evidence-based treatment of gender dysphoria aims to affirm the individual's gender identity through a combination of counseling, exogenous hormones, and sometimes gender-affirming surgery (1). Despite the use of hormone replacement therapy (HRT) for over a century, there is still no consensus on HRT dosing and monitoring for transgender patients (2). Adjustments to HRT regimens in transgender patients are often guided by a given patient's phenotypic response (i.e. bodily changes, undesired side effects, etc.), though the risks and benefits of specific regimens are yet to be completely characterized.

For clarity, the terminology used in this review will include the following: *transgender* refers to individuals who identify as the gender opposite that which they were assigned at birth, whereas *cisgender* refers to those whose gender identity is congruent with that assigned at birth; transgender women or girls (male-to-female) shall be called *MTF* individuals and transgender men or boys (female-to-male) shall be referred to as *FTM* individuals; hormone therapy treatment for gender dysphoria shall be abbreviated *HRT-GD* as opposed to the more general term *HRT*, referring to any patient administered hormones for any reason; *natal male* and *natal female* refer to an individual's gender assigned at birth.

Human breasts are modified epithelial and stromal skin appendages that respond readily to hormonal signals. The incidence of breast malignancies, each with varying degrees of hormone receptor expression, is very high and affects as many as 1 in 9 women during their lifetime (3). The effects of estrogens and androgens on human breast tissue at the macroscopic, cellular, and molecular level have been well investigated in post-menopausal, cisgender women and breast cancer patients, but is unsurprisingly less well understood in transgender patients (4). Transgender patients are often prescribed hormone antagonists in conjunction with HRT, creating a hormonal milieu that has yet to be adequately described in the literature. Given the elevated levels of "opposite" sex hormones, the physiologic effects of long-term HRT warrant future study.

The objective of this paper is to summarize the current data from published literature regarding known effects of HRT-GD along with inter-related endogenous hormones on breast tissue. With the increased availability and utilization of medical and surgical resources to manage gender dysphoria, we hope this review will stimulate further discussion and research into hormone therapy.

2. HORMONE REPLACEMENT THERAPY FOR GENDER DYSPHORIA

Hormonal agents can have profound multi-system effects on individuals receiving HRT-GD. Key recommendations from the 2017 Endocrine Society Practice Guidelines for HRT-GD are summarized in Table 1 (5). Although this provides a general framework for practice, many clinicians have found these guidelines to be lacking in evidence-based recommendations. Table 2 (5–10) includes FDA-reported HRT dosing for cisgender patients compared with typical dose ranges for transgender patients. Of note is the use of antiandrogen agents in the MTF population to reduce the effects of endogenous testosterone. Specifically, although there is concern surrounding the use of prolonged HRT and increased risk of certain malignancies (i.e. adenocarcinoma of the breast), the literature remains unpersuasive.

3. ESTROGEN AND PROGESTERONE

In healthy individuals the hypothalamus releases GnRH in a pulsatile manner, stimulating the anterior pituitary to secrete LH and FSH. In natal males, LH drives Leydig cells to produce testosterone, while FSH induces the differentiation of primary spermatocytes into secondary spermatocytes and facilitates the initiation of spermatogenesis. In natal females, LH supports theca cells that produce androgens and estradiol precursors, while FSH induces ovarian folliculogenesis and follicular maturation. In both biologic males and females, LH and FSH play roles in estrogen, progesterone, and testosterone production that in turn regulate GnRH, LH and FSH primarily through negative feedback.

In natal females, steroid hormones estrogen and progesterone are chiefly synthesized in the ovaries from cholesterol precursors. Ovarian theca cells produce androgens that are then converted to estrogen via aromatase in granulosa cells. In natal males, androgens are converted to estrogen via aromatase in Leydig cells. However, this process only accounts for roughly 20% of estrogens in men, while 80% of estrogen is produced by aromatization of androgens in adipose, brain, skin, and bone tissues (11). Estrogen exists in three forms in the human body: estrone (E1), estradiol (E2), and estriol. The lipophilic nature of these steroid hormones allows them to freely diffuse through cellular membranes and bind to intracellular estrogen receptors (ERs) and estrogen-related receptors (ERRs) such as ERα and ERβ, which are then transported into the cell nucleus. There, the estrogen receptor complex binds to DNA via highly conserved DNA-binding domains, ultimately inducing changes in cellular gene expression (12).

The pattern of nuclear estrogen receptor (nER) expression (i.e., ERα, ERβ, and lesser understood ERRs) on different tissues dictates the effect of estrogen on its target. Membrane estrogen receptors (mERs), which are cell surface G-protein coupled receptors that trigger intracellular signaling pathways rather than directly modifying gene expression, also exist on certain cell types. Mapping studies have utilized chromatin immunoprecipitation (ChIP) in combination with genetic tiling array technology to better elucidate the functions of nERs. Of note, most mapping studies were done with antibodies against ERα, with very limited insight on location and function of ERβ.

In natal males, ERs and progesterone receptors (PRs) have been found on the testes, epididymis, vas deferens, seminal vesicles, efferent ductules, and prostate. In natal females, ERs and PRs have been found on the breast, ovaries, cervix and uterus. As with ERs, PR signaling pathways are complex and can be initiated by activation of nuclear receptors PR-A and PR-B, or exert more rapid effects through activation of membrane bound PRs, cytoplasmic PRs or receptor-independent signal transduction (13).

The combined effects of estrogen and progesterone include, but are not limited to, increased risk of thromboembolic events, development of hepatic adenomas, increased bone density, and cardio-protection. The Women's Health Initiative study on estrogen and progestin hormone replacement therapy in post-menopausal women is perhaps one of the most definitive randomized controlled trials of the modern era. In summary, this study found that despite its reported cardioprotective effects in women, combined estrogen and progestin therapy in healthy post-menopausal women is not recommended for coronary heart disease prevention due to the increased risk of development of invasive breast cancer (14). Interestingly, the use of estrogen without progestin did not significantly increase the risk of breast cancer, even in survivors and patients at a higher baseline risk for breast cancer (15). According to the authors, estrogen-dependent apoptosis reduces breast cancer risk among users of estrogen unopposed by progestins. Similarly, patients receiving progestins alone were not found to have an elevated risk of breast cancer (15). In a more recent study of 290,186 post-menopausal Swedish women (age >39) that used systemic HRT (estrogen with or without progestins), breast cancer risk was elevated in both groups compared to women who did not use HRT (16). However, the overall cancer risk was only slightly higher in the HRT cohort as patients taking HRT had a *lower* risk of gastrointestinal malignancies. These conflicting findings are further complicated by data that show synthetic progestins have differing effects than endogenous progesterone when binding PRs, as discussed later. Despite such extensive research on the effects of these hormones in biological females, their effects on transgender patients remains largely unexplored.

Estrogen and Progesterone in the Breast

Estrogen plays a critical role in human breast development, inducing the growth of breast ducts, increasing fat deposition, and promoting breast stromal connective tissue growth. Estrogen upregulates PR expression and induces prolactin, which works in conjunction with progesterone to stimulate breast lobuloalveolar development (12).

Given the role of both estrogen and progesterone in breast development, researchers have done extensive work to better understand the role of hormones in breast cancer. In addition to the JAMA-WHI, Nature and Swedish studies referenced, a number of studies have corroborated the association between HRT and breast cancer in postmenopausal women. HRT (both estrogen-only and combination estrogenprogestin) has been linked with an elevated breast cancer risk, dependent on duration of therapy. This effect is reduced after discontinuation of HRT and becomes insignificant 5 years after cessation (17). The applicability of these conclusions to transgender women should be questioned, given the altered breast anatomy and complicated hormonal milieu among biological males taking

estrogen and/or androgen-suppressing agents, some of whom retain endogenous testosterone production.

Estrogen and Anti-androgen Therapy for Transgender Women

Current guidelines support the use of estrogen therapy in adult MTF patients and in adolescent MTF patients undergoing GnRH agonist therapy to halt initiation of puberty. The goal of maintenance estrogen therapy is to suppress development of unwanted secondary sex characteristics in adolescent MTF patients, and to repress these characteristics in adult patients. Estrogen therapy alone negatively feeds back on the hypothalamic-pituitary axis, leading to decreased testosterone production in MTF patients to low-normal ranges for biological males (200–300ng/dL), but not to the normal testosterone levels of natal females (75ng/dL) (18). Therefore, most MTF patients use anti-androgen agents such as spironolactone and cyproterone in conjunction with estrogen to achieve even lower testosterone levels. To date, no studies have been published on the effects of longstanding estrogen therapy on transgender women.

4. TESTOSTERONE

Testosterone, the primary sex hormone in natal males, is synthesized primarily by the Leydig cells of the testes, following a biosynthetic pathway that begins with cholesterol as the precursor. Dehydroepiandrosterone (DHEA), an intermediate steroid along this pathway, can be converted to androstenedione and then to testosterone. In natal females, low levels of testosterone are produced by the ovaries. Additional testosterone is converted from estradiol in the liver via reverse aromatization and is produced in small amounts by the adrenal glands in both sexes. Androgen receptors (AR), also known as NR3C4 (nuclear receptor subfamily 3, group C, member 4), are activated by binding of androgenic hormones (testosterone or dihydrotestosterone) in the cytoplasm of target cells. As with nERs, the ligand-AR complex then translocates to the nucleus where it regulates gene expression as a transcription factor, influencing the development of secondary male sex characteristics, increasing muscle mass, as well as bone growth and mineralization.

Androgen Therapy in Transgender Men

Testosterone is an important hormone for FTM patients seeking physiologic masculinization. Typically, the desired effects are body and facial hair, voice deepening, increased muscle-fat ratio, clitoral hypertrophy (formation of a “micropenis”), and reversal of the effects of endogenous female sex hormones, including cessation of menstruation. Testosterone cypionate, the ester of testosterone, was introduced in 1951 and is commonly used in the United States due to its properties as a long-lasting prodrug with a half-life of 8 about days when injected intramuscularly. Dosing typically starts around 50 mg every 2 weeks with gradually escalating doses, similar to the treatment of hypogonadism in cisgender men (up to 200 mg IM every 2 weeks) (19). Other forms of testosterone used include testosterone enanthate, testosterone undecanoate, and testosterone propionate. Because enteral bioavailability is low, most forms of testosterone are given as subcutaneous pellets, intramuscularly, or topically. Hormone levels are measured to ensure dosage titrations achieve the desired circulating hormone levels.

As previously discussed, testosterone is aromatized from estradiol into biologically-active estrogens primarily in adipose cells, with increased adipose tissue resulting in greater amounts of conversion (20). Exogenous testosterone causes a drop in *endogenous* estrogen concentration, along with a decrease in sex hormone-binding globulin (SHBG), gonadotropins (LH, FSH), and prolactin (19). Because androgens are a substrate for estrogen synthesis by aromatization in peripheral tissues, treatment of estrogen-receptor-positive breast cancers often employs aromatase inhibitors. This approach is limited to post-menopausal or oophorectomized women in whom the synthesis of estrogen by the ovaries is no longer the primary source of this hormone. One can thus think of testosterone as an estrogen precursor, and furthermore as an endogenous source of estrogen production even in patients without ovaries. In post-oophorectomy FTM patients receiving exogenous testosterone (with dosing adjusted to achieve normal male serum testosterone concentrations), estradiol levels are comparable to those in natal men. In FTM patients receiving HRT who have not undergone gonadectomy, circulating estradiol levels do not increase, reflecting the impact of suppression of native estrogen production rather than an increase in peripheral estradiol production by aromatization (21).

Effects of Testosterone on the Breast

Therapeutic doses of testosterone lead to a decrease in breast glandular tissue and overall adipose tissue, as well as an increase in breast fibrous connective tissue (22,23). Increased breast parenchymal density (possibly related to elevated levels of free endogenous sex steroids) has been linked to increased breast cancer risk (16), but this should not be confused with the increase in fibrotic tissue density observed in patients receiving androgens. With or without mastectomy, most studies suggest that testosterone therapy leads to a *reduction* in breast cancer risk (23). The authors postulated that because testosterone has been shown to inhibit estradiol-induced mammary epithelial proliferation, block estradiol-induced ERα expression, and promote breast epithelial cell apoptosis, elevated testosterone levels (even in the presence of elevated estrogens by action of testosterone aromatization) prevents estradiol from exerting its full biologic effects. The resultant mammary tissue histologically resembles postmenopausal breast tissue. A Dutch study retrospectively showed no cases of breast cancer among 795 FTM patients starting HRT at an average age of 23 and for a mean of 20 years, which was calculated as an incidence of 5.9 cases per 100,000 person-years in FTM patients compared to 154.7 cases per 100,000 person-years in cisgender women (24).

Testosterone therapy is typically used as a single agent in FTM patients (19). Like estrogen HRT-GD in MTF patients, exogenous testosterone leads to negative feedback on hypothalamic-pituitary axis resulting in a decrease in estrogen and prolactin production. Studies investigating a link between physiologic levels of testosterone and cardiovascular risk are inconclusive, however, there is a well-established risk of absolute polycythemia seen with testosterone HRT-GD, requiring periodic surveillance.

5. BREAST PATHOLOGY IN TRANSGENDER PATIENTS

A meta-analysis published in the *European Journal of Surgical Oncology* in 2018 summarized 18 articles which described a total of 22 breast cancer events (median age of

51.5 at diagnosis) in MTF patients. Of the 22 cancers, there were 13 adenocarcinomas (8 invasive ductal carcinoma and 5 not otherwise classified), 3 breast implant-associated anaplastic large cell lymphomas (BIA-ALCL), 1 ductal carcinoma-in-situ (DCIS), 1 mixed invasive ductal / Paget's disease of the breast, 1 malignant phyllodes tumor, 1 secretory tumor, and two unspecified. The most common symptom at presentation was a breast lump. 10/19 breast cancers expressed estrogen receptors (ER+) and 5/14 were PR+. Family history of breast cancer was reported by seven patients (one BRCA2+) (25).

A follow up to the meta-analysis included 8 articles and described a total of 17 FTM patients with breast cancer (median age at diagnosis 44.5). Four occurred after prior masculinizing chest procedures and three were incidental findings at the time of gender-affirming mastectomy. All but two received testosterone HRT (duration 18 months -to 15 years). Invasive ductal carcinoma was found to be the most common type (n=8), followed by unspecified (n=7), and lobular carcinoma (n=2). 12 out of 14 cancers were ER+ and 9 were PR+. A breast lump was the most common presentation (26). In the experience of the senior author (ECR), one such FTM patient was incidentally diagnosed with lobular carcinoma in-situ at the time of gender-affirming mastectomy after 20+ years of androgen use, but many others were found to exhibit atypia or hyperplasia of their breast tissue.

6. OTHER SUBSTANCES INFLUENCING BREAST TISSUE

Growth Hormone and Insulin-Like Growth Factor

Growth hormone (GH), also known as human growth (hGH) or somatotropin, is a peptide hormone synthesized and secreted by somatotropic cells in the anterior lobe of the pituitary. Insulin-like growth factor 1 (IGH-1, somatomedin C) is the main effector of GH and is produced mainly by the liver, but is also synthesized by other organs in a paracrine/autocrine fashion (27).

When GH binds a GH receptor (GHR) on target cells, the receptors dimerize and activate Janus kinase 2 (JAK2), an intracellular, nonreceptor tyrosine kinase that triggers multiple signaling pathways, including epidermal growth factor receptor kinases, members of the mitogen-activated protein (MAP) kinase family, members of insulin receptor substrate (IRS) family, and the Signal Transducers and Activators of Transcription (STAT) family. Collectively, these pathways regulate cell proliferation, metabolism and tissue inflammation (28).

GH, IGF-1 and Breast Development

IGF-1 and GH contribute to breast development by stimulating glandular cell hypertrophy and epithelial proliferation in a dose-dependent fashion. Deficiencies in either of these hormones or defects in their receptors have been correlated with diminished or absent breast growth in natal females. Even when GH is present, there is no mammary development without IGF-1 (29). During puberty, levels of sex hormones increase, which stimulate an increase in GH, leading to the development of secondary sexual characteristics (30). After puberty, IGF-1 and GH levels gradually diminish, which has been a postulated cause for less

dramatic breast development in MTF patients who initiate HRT-GD many years after puberty. Exogenously IGF-1 and GH stimulate mammary hyperplasia in animal models (31).

However, transgender patients (both FTM and MTF) receiving HRT-GD typically exhibit an increase in IGF-1 during the first three months of treatment (30). Estradiol directly increases the expression of IGF-1 (32,33). Progesterone acts by a similar mechanism, also enhancing the production of IGF-1, leading to ductal morphogenesis (34). Studies involving transgenic mice overexpressing IGF-1 have shown that elevated levels lead to ductal hypertrophy in lactating mice, and prevents post-lactational mammary gland involution (35). Knock out of IGF-1R or the GHR in female mice leads to ductular growth failure, which is comparable to the effects produced by the knockout of estrogen receptors (ER), as expected.

GH and IGF-1 Effects on Pathology

GH & IGF-1 have anti-apoptotic and mitogenic activity [28, 30]. There is evidence that some neoplastic progression, for example in prostate cancers, are associated with increased IGF-1R expression (36,37). Elevated GHR expression in breast tumors has been correlated with elevated PR expression (38).

Prolactin

Prolactin, also known as luteotropic hormone or luteotropin, is a peptide hormone that stimulates lactation in mammals, promotes breast tissue development (39) and is responsible for a number of other functions and systems involved in growth, development, metabolism, and immune system regulation (40). Prolactin is stored and secreted by lactotropic cells in the anterior pituitary, as well as in the decidua, myometrium, lymphocytes (41) in breast glandular and adipose tissue, peripheral adipose tissue (42), hair follicles, skin (43), and the prostate (44). Prolactin secretion is regulated by the hypothalamus. Dopamine decreases prolactin secretion up to 10-fold (39). Prolactin receptors (PRLRs) are found mainly in the epithelium and stroma of the breast (45) and ovaries, but also to a lesser degree in other organs (46). When prolactin binds to a PRLR, the receptor dimerizes, activates the JAK2/STAT signaling pathway, and ultimately leads to gene transcription (40,47).

Prolactin and Breast Development

Prolactin itself does not directly stimulate breast development but rather increases ER and PR expression, as well as the endogenous synthesis of both hormones. Prolactin also decreases the expression of androgen receptors and down-regulates androgen synthesis in breast cells. The combined effect of elevated prolactin levels in natal males is gynecomastia (48,49). Experimental use of a dopamine antagonist (Perphenazine) in rats led to a 5 to 10-fold rise in serum prolactin at two days post-treatment, and a 3 to 4-fold increase in breast prolactin was noted at day four. Mammary tissue volume continued to increase up to day 14, reaching an 8.9-fold peak (50).

GnRH agonists

Leuprolide, goserelin, and histrelin are used in peri-pubertal individuals of both sexes to suppress or arrest puberty in a reversible fashion (51). These can also be used as an anti-androgenic agent in conjunction with estrogen therapy in adult MTF patients (18). The

mechanism of GnRH agonist action relates to the relatively stable serum levels of these exogenous agents (in contrast to endogenous pulsatile secretion by the hypothalamus). This downregulates production of LH and FSH by the anterior pituitary and thus downstream estrogen, progesterone, and testosterone synthesis.

Androgen Receptor Blockers

Flutamide, an antiandrogen used as monotherapy in patients with prostate cancer, leads to gynecomastia development in 30 to 76% of treated men (52). MTF transgender patients may use this medication at doses of 50–75 mg day (53). Spironolactone blocks androgens from binding to their receptors, and increases both total and free estrogen levels, resulting in anti-androgenic properties (54). Cyproterone acetate is used in MTF patients at doses of 50–100 mg day (53). This drug has a stronger anti-androgenic effect than spironolactone but carries a significantly greater risk of adverse effects including depression and meningioma (at doses exceeding 25mg/day) (51,55).

Progestin

Synthetic progestogens (progestins) such as norethisterone, medroxyprogesterone, and lynestrenol, bind to PRs but do not perfectly mimic progesterone and can activate or antagonize other types of steroid hormone receptors (13). Progestins are often prescribed to suppress menses in FTM patients. Studies have shown that these drugs cause a drop in serum levels of SHBG and LH, but significantly increase free testosterone. Estrogen, FSH, and total testosterone, however, do not change significantly (56). As discussed above, progesterone activity on breast tissue includes lobuloalveolar maturation in conjunction with prolactin and, to a much lesser degree than estrogen, ductal development.

Side Effects

Breast tissue hypertrophy is a rare side effect of a variety of drugs that span multiple classes. A summary of common drugs that have been reported to cause breast hypertrophy are summarized in Table 3 (57–68). Other medications that are not listed include misoprostol, ranitidine, cimetidine, and omeprazole. Of those mentioned, high-dose cimetidine (>1000mg/day) over a long period increases the risk of breast hypertrophy the most (40x) (69,70).

7. HEALTHCARE DISPARITIES

The effective clinical study of HRT-GD regimens is hampered by barriers to trust and information sharing between physicians and transgender patients who have historically suffered from significant disparities in access to healthcare. Disenfranchisement can be at least partially attributed to a distrust that developed within the transgender community towards healthcare providers during the AIDS crisis (71). Multiple studies have reported a particularly high rate of HIV/AIDS among MTF patients, approaching 20% in some parts of the world, adding unneeded stigma to an already marginalized population. (72). The validity of these numbers have been debated by some who point out that such studies often disproportionately survey sex workers, who are at increased risk due to the nature of their profession (73). Although sampling bias may be one explanation for the reportedly high

prevalence of HIV infection, other authors argue that a significant percentage of transgender women engage in sex work due to poor job prospects stemming from societal alienation. Other socioeconomic consequences include underemployment, homelessness, substance abuse, as well as poor access to healthcare (71,74–80). More recent studies addressing barriers to healthcare access suggest that there is a shortage of providers who are knowledgeable on transgender health needs such as HRT-GD (81,82). Although very few studies to date have polled practicing clinicians, surveys of medical students and residents suggest that there is a subjective deficiency in how doctors are educated in appropriate HRT-GD prescribing practices (83,84). Hormone therapy is an important cornerstone of gender dysphoria management, and this gap in medical education likely contributes to the difficulty transgender patients experience in finding providers who understand their unique needs (81). When there are financial or socioeconomic obstacles to obtaining HRT-GD, transgender persons are more likely to seek out unregulated, unlicensed black market dispensaries to get HRT (85).

While the World Professional Association for Transgender Health (WPATH) and similar organizations provide a forum for evidence-based healthcare guidelines, there is a lack of consensus in HRT-GD prescribing practices as well as long-term preventative breast care for transgender patients. Among the most pressing issues are screening guidelines for breast and reproductive organ cancers. Conversations between providers and transgender patients about the long-term risk of breast cancer are often incomplete due to the lack of robust scientific data to address this question. Consistent prevention-centered practices are further complicated by wide regional variability in state-mandated insurance coverage of medical and surgical treatments for gender dysphoria in the United States, which may disincentivize providers from offering such services.

MTF individuals experience variable degrees of breast development due to HRT-GD while FTM patients typically have residual breast tissue for both inadvertent (technical) and intentional (aesthetic) reasons after complete mastectomy. Both patient populations are at some risk for developing breast cancer and deserve surveillance guidelines to establish the best screening tools and the frequency of testing (86). Mammography is difficult in this population, as most FTM patients do not have sufficient breast tissue for standard mammographic procedures to be useful (26). In an analogous sense, MTF patients undergoing gender-affirming “bottom surgery” (e.g., penectomy, orchiectomy and vaginoplasty) typically still have a prostate gland with the potential to develop future malignancy. Prostatectomy is not routinely performed in gender-affirming bottom surgery due to the risk of incontinence and other morbidity (87). The fact that many FTM patients still have some or all of their natal internal reproductive organs (i.e., uterus, ovaries and adnexa) even after transition, poses additional questions of how to perform routine gynecologic surveillance. To address breast, gonadal and prostate health risks, which may be altered by HRT-GD, consensus guidelines are needed so that surgeons and physicians can properly educate patients and close the health disparity gap affecting so many transgender individuals.

8. CONCLUSIONS

The use of HRT and sex hormone modulators has become a mainstay of therapy in patients with gender dysphoria. Numerous substances, both exogenous and endogenous, can stimulate breast hypertrophy. The long-term effects of pharmaceuticals used off-label for modulation of hormone levels and sexual characteristics in transgender patients have not been sufficiently studied. The propensity of hormones to promote the growth of certain cancers also raises questions about appropriate dosing and the safety of drug combinations. Further clinical and laboratory study is needed to better establish safety and dosing guidelines in transgender patients as well as routine breast surveillance guidelines for this population.

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Table 1.

Summary of Key Recommendations from the 2017 *Endocrine Society Practice Guidelines* for HRT-GD

Adolescents	GnRH analogues may be used in adolescents after they begin exhibiting signs of puberty
	Beginning HRT-GD after age 16 has been studied, though there may be compelling reasons to initiate hormone therapy prior to age 16
	Clinicians should monitor clinical signs of puberty development every 3–6 months and laboratory values every 6–12 months during therapy
Adults	Laboratory monitoring every 3 months for the first year of treatment, then 1–2 times annually
Surveillance for Adverse Outcomes	MTF patients *without* increased baseline risk for breast cancer should undergo the same breast cancer screening guidelines as cisgender females
	Prolactin levels should be monitored periodically for MTF patients
	Patients with elevated risk of developing osteoporosis should be assessed for bone mineral density

Table 2:

Comparison of Recommended HRT Dosages in Cisgender and Transgender Individuals

HRT for Postmenopausal Cisgender Women (6–8)	HRT-GD for MTF Individuals (5,7)
Oral Estrogen • Oral Conjugated Estrogen: 0.625 mg / day * • Oral 17-β Estradiol: 0.5 – 1mg / day *	**Oral Estrogen** • Oral Conjugated Estrogen: 2.5 – 7.5mg / day • Oral 17-β Estradiol: 2 – 6mg / day
Parenteral Estrogen • IM Estrogen (Valerate): 10 – 20mg IM every 4 weeks • IM Estrogen (Cypionate): 1 – 5mg IM every 3–4 weeks	**Parenteral Estrogen** • Estradiol Valerate: 5 – 20mg IM every 2 weeks • Estradiol Cypionate: 2 – 10mg IM every week
Transdermal • Estradiol Patch: 0.0375 – 0.05 mg / day (patch changed weekly) *	**Transdermal** • Estradiol Patch: 0.1 – 0.4mg / day (patch changed weekly)
Antiandrogen • N/A	**Antiandrogen** • Spironolactone: 100–200mg PO / day (400mg max) • Cyproterone acetate: 50–100mg PO / day • GnRH Agonist: 3.75mg SQ / month • Finasteride: 1 – 5 mg PO / day
HRT for Cisgender Men (9)	**HRT-GD for FTM Individuals (5,10)**
Oral • Mucoadhesive “Buccal” Testosterone: 30mg BID *	**Oral** • Testosterone Undeconate: 160 – 240mg / day †
Parenteral • Testosterone Enanthate: 50–200 mg IM every 2–4 weeks * • Testosterone Undeconate: 750 mg IM every 10 weeks after two initial loading doses 4 weeks apart *	**Parenteral** • Testosterone Enanthate: 20 – 100 (avg 50) mg IM/SQ / week • Testosterone Undeconate: 750 mg IM every 10 weeks ‡ • Testosterone Cypionate: 20–100 (avg 50) mg IM/SQ / week
Transdermal • Testosterone Gel: 40–50mg / day * • Testosterone Patch: 4mg / day *	**Transdermal** • Testosterone 1% gel: 12.5 – 100 (avg 50) mg / day • Testosterone Patch: 1 – 8 (avg 4) mg / day

* Risk and benefit profiles at this dosage for hypogonadism have been studied and validated in prior studies.

† Very low bioavailability in oral form, must be taken several times per day.

‡ Use is restricted in the United States, must be administered in an office or hospital setting to monitor for adverse reactions.

Table 3.

Medications Known to Cause Breast Hypertrophy

Type	Examples	Mechanism of Action	Reference
Calcium Channel Blockers	Amlodipine Diltiazem	Unknown (elevated levels of prolactin have been found)	48
Statins	Atorvastatin	Suppression of gonadal and adrenal steroid hormone synthesis	49
Angiotensin Converting Enzyme Inhibitors	Captopril enalapril	Unknown	50
Cardiac Glycosides	Digoxin	Structurally similar to estradiol; bind ERs in breast tissue	51
5α-Reductase Inhibitors	Finasteride Dutasteride	Block conversion of testosterone to dihydrotestosterone, elevating the estrogen to androgen ratio	52, 53
Antiretrovirals	HAART Efavirenz	Increase in interleukins (IL-6) and aromatase activity, increasing free estrogen and direct binding of ERα in breast tissue	54, 55
Antifungals	Ketoconazole	Anti-androgenic; competitively blocks steroid from SHBGs and thus increases free dihydrotestosterone and estradiol	56
Antibiotics	Metronidazole Isoniazid	Unknown	57–59