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Review

Emerging and accumulating safety signals for the use of estrogen among transgender women

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Abstract
Efforts to alleviate the psychological distress of gender dysphoria have included the use of exogenous estrogen (often with anti-androgens) to alter secondary sex characteristics of natal males. In response to the rapid increase in presenting cases among young people, extensive scrutiny has now been brought to bear on these medical interventions for minors, with ESCAP reporting "an urgent need for safeguarding clinical, scientific, and ethical standards." However, due to the lack of systematic outcome data, the associated risk–benefit profile is unknown. Several recent systematic reviews have found the evidence of benefit to be of low or very low certainty, while some risks, such as infertility, have been long recognized. This paper compiles several emerging and accumulating safety signals in the medical literature. These range from increased rates of previously associated adverse outcomes with long-term estrogen use (e.g., acute cardiovascular events) to associations of estrogen use with newly identified adverse outcomes. Estrogen also induces changes in the brain, raising concerns for negative impacts on mood (e.g., depression) and cognition. These safety signals indicate the need for further investigation and a thorough systematic search for others, which may now be more evident due to the increased number of young people receiving these treatments. There is an urgent need for the evidence base to be improved with more studies, especially those with systematic long-term follow-up and those that can disentangle possible confounders, as well as systematic reviews to help interpret their reliability.

1 Introduction

The recent European Society for Child and Adolescent Psychiatry (ESCAP) policy statement regarding care for adolescents and children with gender dysphoria calls for "safeguarding clinical, scientific and ethical standards" [1]. In particular, they call for adherence to "the core professional and medico-ethical principles" (p. 2012) of non-maleficence, beneficence, autonomy, and justice. These principles incorporate ethical, informed consent and require reliable, up-to-date information in support of informed comparisons of benefits and harms by the patient, the parents, and the physician. The focus of this paper is on harms associated with the use of exogenous estrogen (often with anti-androgens) [2, 3] to treat gender dysphoria or being transgender. It does not compare different treatments for gender dysphoria or the behavior of gender dysphoria over time.

For gender dysphoria, weighing treatment options in accordance with the four key medico-ethical principles is challenging. Although the etiology of gender dysphoria and its progression in the absence of medical intervention (including its likelihood of resolution) is not well understood [1, 4, 5], gender medical interventions for minors were extended to general clinical settings after being introduced as part of "innovative research practices" [6]. Medical best practices

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(currently evidence-based medicine) are now being brought to bear regarding these interventions. Reasons include the recent and not fully understood rapid rise in those presenting with gender dysphoria or trans-identification (primarily minors and young adults), the disagreement among professionals, and increasing reports of harm related to transition [4, 7, 8]. Evidence-based medicine includes guidelines based on systematic reviews of the evidence [4, 9]. Recent systematic reviews have found low or very low certainty evidence for many outcomes of hormone use for minors [4, 10–13]; see also [14–16]; see also [17], which appeared as this paper was completing review.

For benefit from hormones across all ages, Baker et al. [18] found low-quality evidence regarding effects on depression, anxiety, and quality of life and insufficient evidence to draw any conclusion regarding the effect on death by suicide (possible evidence ratings were high, moderate, low, or insufficient). For estrogen specifically, a Cochrane review [19] found no qualifying completed studies. A recent (highly publicized) 4-center study of short-term outcomes of adolescents [20] found no psychosocial improvement among natal males (see [21–24] for further discussion). Among adults, Bränström and Pachankis [25] found no benefit to hormones (or, once corrected, surgeries [26]) for any of their outcome measures. Study limitations include a lack of randomized prospective trial design, small sample sizes, recruitment biases (see, e.g., D'Angelo et al. [27]), premature follow-up, high dropout rates, psychometrically inadequate measurement instruments, uncontrolled confounding, and/or the lack of appropriate controls.

Regarding risks, the Endocrine Society's 2017 guidelines state there is a need for "rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols," and that future "endocrine treatment protocols for GD/gender incongruence should include the careful assessment of: [...] the risks and benefits of gender-affirming hormone treatment in older transgender people" ([3], p. 3874). Risks for transgender adults are relevant for minors as well, as hormone use is expected to be lifelong for those who experience a long-term transgender identity. The most recent World Professional Association for Transgender Health (WPATH) recommendations [2] list several previously observed associated harms. WPATH commissioned systematic reviews of the evidence to study risks such as those to the cardiovascular system, reproductive tissue, the endocrine system, and fertility [28]. While these reviews have been completed, their findings have not been released. In addition, as the US FDA has not established that the benefits outweigh the risks, these drugs do not have FDA approval for treating gender dysphoria.

However, these previously associated risks associated with estrogen as a treatment for gender dysphoria do not seem widely known to clinicians treating this population or to the patients themselves, which undermines ethically necessary informed consent [5]. In fact, leading gender-affirming experts have even asserted that gender-affirming hormone therapy (GAHT) "effects are primarily cosmetic" (Turban and Keuroghlian [29], p. 453) and that there are "no clinically significant adverse effects with gender-affirming sex hormones" (Rosenthal [30], p. 587). Beyond the previously identified harms associated with estrogen use by transgender women, many new safety signals are appearing; these are the focus here. They include exacerbation of some previously identified harms associated with long-term use.

Historically, far fewer people identified as transgender [31], and even smaller numbers sought medical intervention [1]. Due to the recent surge of patients—including and especially among minors [32, 33]—who identify as transgender and are subsequently medicalized, signals from associated adverse reactions have become more detectable. These emerging safety signals warrant a better understanding of their frequency, severity, and permanence, as well as searches for others. This paper aims to motivate such efforts in addition to informing clinicians and researchers of these particular associated adverse outcomes.

To identify risks of harm, the starting points used were "clinically significant" effects together with "likely increased risk" in WPATH recommendations (Coleman et al. [2], p. S254) (these overlap with the "serious health consequences" noted by ESCAP (Drobnič et al. [1], p. 2012]), estrogen risks for older women, and anecdotal reports of medical problems with the transgender community including personal interviews with three detransitioned transwomen. Medical risks have contributed to the decision to detransition for some [34].[1] Below, we discuss studies and reviews regarding these safety signals, summarize several observed effects of and associations with estrogen on the male brain, and conclude with a discussion. We observe that patients in studies may be receiving anti-androgens simultaneously.

[1] Uncontrolled studies are unfortunately common in this field, for example, the studies whose claimed benefits [35, 36] were used as justification for medical intervention in the Endocrine Society guidelines [3] were also uncontrolled.

2 Some previously identified adverse physiological effects associated with estrogen

Infertility and venous thromboembolism (VTE) are the two previously recognized risks described by Coleman et al. [2] as both clinically significant and with "likely increased risk" (p. S254). These risks are also highlighted by ESCAP [1]. Some risks, such as infertility, are not generally expected in the absence of treatment. There are also previously recognized estrogen risks ("box warning") for older women, including stroke, deep vein thrombosis, and probable dementia [37].

2.1 Fertility risks

Several studies report that some fraction of patients have preserved spermatogenesis (e.g., 24% [38], see also [39, 40]), while others have "complete cessation of spermatogenesis with testicular atrophy, hyalinization, and fibrosis" [41], p. 211, see also [42]). A recent systematic review also reported atrophic testes having "smaller seminiferous tubules with heavy hyalinization and fibrosis… Oestrogen and anti-androgen treatment causes higher proportions of sperm abnormalities (i.e., low total sperm count, low sperm concentration, poor sperm motility) or azoospermia; however, some of these effects seem to be reversible upon cessation" [40], p. 184. Sperm motility reports were varied, with moderate to severe effects noted for at least some patients; one study found significant reductions for those currently taking hormones [41, 43]. See also [44, 45].

An analysis of patients who had undergone gender-affirming orchiectomy identified atrophic changes, decreased spermatogenesis, reduced mean tubule diameter with basement membrane thickening, maturation arrest and aspermatogenesis, with 65% showing germ cell nucleomegaly with cytological atypia mimicking germ cell neoplasia in situ [46] (see also [47, 48] and the studies on the risks of testicular cancer below).

2.2 Cardiovascular risks

Research consistently indicates that transgender women undergoing feminizing hormone therapy face increased cardiovascular risks compared to reference populations like non-TGNB men not using hormones [49–52]. The most frequently cited concerns are venous thromboembolism (VTE) and stroke.

Multiple studies and reviews have quantified the elevated risk of VTE, although the reported magnitude varies. For instance, a meta-analysis involving over 15,000 transgender women found their VTE incidence was 2.2 times higher than that of non-TGNB men [50]. One narrative review [51] concluded there was "strong evidence that estrogen therapy for trans women increases their risk for venous thromboembolism over fivefold" (p. 243). Extrapolating from studies of hormone therapy in postmenopausal women, the review concluded that transdermal estrogen possibly carries a lower risk for VTE than orally-administered estrogen. The increased risks of VTE could be a result of the procoagulant effects of feminizing GAHT, with transdermal estrogen exhibiting lower procoagulant effects [53]. Another review calculated an odds ratio of 2.23 (95% CI 1.93–2.57, $p < 0.001$) for thrombosis in transgender women compared to non-TGNB men [52]. Notably, a large cohort study following 2517 transgender women for an average of about 9 years reported a standardized incidence ratio (SIR) for VTE of 4.55 compared to non-TGNB men [54].

Several studies have also documented an increased risk of stroke. The abovementioned meta-analysis by Van Zijverden et al. [50] also reported a 30% higher incidence of stroke among transgender women compared to non-TGNB men. The long-term cohort study by Nota et al. [54] found a stroke SIR of 1.80 (95% CI 1.23–2.56).

Emerging evidence suggests that cardiovascular risks escalate significantly with prolonged estrogen use. A large US cohort study tracked risks over time [55]. In the first 2 years, VTE incidence was 50% higher, and in the first 6 years, ischemic stroke incidence was 30% higher compared to non-TGNB men. However, the risk increased substantially after these initial periods: VTE incidence became 5.1 times higher after 2 years, and ischemic stroke incidence rose to nearly 10 times higher after 6 years [55]. The authors conclude there is a "need for long-term vigilance in identifying vascular side effects of cross-sex estrogen" (p. 205); a similar discussion is echoed by [56] with a reference to [57] as well. While the Van Zijverden et al. [50] meta-analysis (supplemental material 3 in [50]) considered [54, 55] to be at risk of bias, including confounding bias, it nonetheless found the higher stroke and VTE incidences above. Comparisons within the already available data of [55] might be able to address some of its confounding concerns, as might other studies. There are also shorter term studies, comparisons with other treatment groups and comparisons of other outcomes including [58–60].

A transgender woman on transdermal estradiol gel hormone replacement therapy experienced a sudden loss of vision and metamorphopsia due to branch retinal vein occlusion (BRVO) [61]. The authors concluded that as "estrogen

increases cardiovascular risk when used in hormone replacement therapy, RVO is a complication that must be taken into account…especially in transgender women (male-to-female) who are more at risk."

2.3 Cognitive impairment

A systematic review of cognitive impairment among young transgender adults [62] found no effect of hormones on a total of 162 trans women across 8 studies, with 10 to 31 people in each sample exposed to treatment (time on hormones unspecified). However, a study with a larger sample size (73) with long-term follow-up (average 25.8 years) found that transgender women (56–84 years) who had been on GAH had lower scores than both non-TGNB men and women (matched in education and age) in information-processing speed and episodic memory [63]. There is a known doubling of relative risk for probable dementia after an average follow-up of 4 years for older women, listed as a serious risk in the FDA insert for estrogen [64]; risks for younger women were not studied. A study that did not report hormone usage found that 14% of transgender and nearly 17% of non-binary adults over 45 in the 2016–2018 Behavioral Risk Factor Surveillance System (BRFSS) survey reported subjective cognitive decline (or SCD) as compared with 10% for those not of a gender minority [65].

3 Emerging safety signals: other associated adverse physiological effects

3.1 Overall health risks and early mortality

In a retrospective Dutch population cohort study of patients who visited the Amsterdam gender identity clinic (treating 90% of the Dutch transgender population) over five decades, the all-cause mortality risk of transgender women on hormones was much higher than the general population [66]. The overall survival odds of transgender women started to deviate from general population men or women within a few years of starting GAH therapy, and the difference increased monotonically over time. The overall mortality risk of transgender women, as measured via the standardized mortality ratio (SMR), was higher compared to men in the general population (SMR 1.8, 95% CI 1.6–2.0) and even higher compared to women. The major causes of death included cardiovascular disease (21%), cancer (32%), infection-related disease (5%), and suicide (7.5%). Note that a recent Finnish record study found that suicide rates of young people were correlated with psychiatric morbidity (as measured by specialist psychiatrist visits) rather than gender dysphoria diagnosis or associated medical interventions [67].

An earlier study of 966 transgender women (who appear to be a subset of the patients in [66]) found a mortality rate 51% higher than in the general population [68]. Lung and hematological cancer mortality rates, but not total cancer mortality rates, were elevated. Current but not past estradiol use was associated with a threefold increased risk of death from cardiovascular events.

It is harder to interpret findings of studies that do not specify which transgender patients use hormones, such as the earlier mortality observed for transwomen in 2011–2019 American private insurance data (starting around age 30 [69]) and in a UK longitudinal study [70], and higher incidence of chronic conditions and higher observed rates of "potentially disabling mental health and neurological/chronic pain conditions, as well as obesity and other liver conditions (non-hepatitis)" than non-TGNB US Medicare beneficiaries [71].

3.2 Autoimmune disease

Possible increased autoimmune disease risk for transwomen taking estrogen has been discussed [72]. Salgado et al. [73] reviewed several case studies of transwomen with immune-mediated rheumatic diseases: rheumatoid arthritis (1), ankylosing spondylitis (1), systemic lupus erythematosus (SLE, 4), skin lupus erythematosus (1), and systemic sclerosis (4). A transwoman with previously limited and contained skin-related systemic sclerosis (SSc) suddenly had her condition develop into scleroderma renal crisis, a life-threatening complication with the abrupt onset of severe hypertension accompanied by rapidly progressive renal failure, with the authors concluding "estrogen supplementation could play a pathogenic role in SSc and its diverse complications" (Arneson and Varga [74], p. S355).

A retrospective cohort study of (English) Hospital Episode Statistics from 1999 through 2012 matched to population controls found males with gender identity disorders (hormone usage unspecified) had an adjusted rate ratio of multiple

sclerosis (MS) of 6.63 (95% CI 1.81–17.01, p = 0.0002) and "a potential role for low testosterone and/or feminizing hormones on MS risk" (Pakpoor et al. [75], p. 1759).

3.3 Diabetes

A systematic review [76] found that estradiol, with or without anti-androgen, decreases lean mass, increases fat mass, and may worsen insulin resistance. HOMA-IR values, a measure of insulin resistance that presages diabetes, increased by 72% in the first year of treatment and 9% more in the second year, relative to baseline, for 79 healthy (at baseline) subjects followed for 2 years [77]. A recent narrative review found that feminizing hormone therapy is associated with higher fat mass and insulin resistance [49]. A recent systematic review [78] of 11 studies, including [76], found increased insulin resistance in transgender women on GAH compared to controls. They also mention the possibility of increased risk over longer durations.

3.4 Pancreatitis

A case report [79] noted that estrogen therapy in transgender women could be an under-recognized cause of elevated triglyceride levels, possibly putting this group at a higher risk for severe pancreatitis. Another case study of gallstone pancreatitis concluded that estrogen therapy among transgender women is a "likely risk factor for the development of gallstone pancreatitis" (Freier et al. [80], p. 1674).

3.5 Thyroid cancer

Experimental studies indicate a possible role of estrogen in the pathogenesis of thyroid cancer (see, for example, Derwahl and Nicula [81]). Thyroid cancer prevalence in US military veteran transgender women records was 0.34% (34/9988 TW) compared to 0.19% of non-TGNB men and 0.64% of non-TGNB women [82]. 11 of the 34 patients had been taking estrogen for an average of 3.4 years before their diagnosis, with a higher incidence of Hürthle cell cancer (which has lower survival rates than papillary thyroid cancer) than in the general population.

3.6 Testicular cancer

Several studies have reported outcomes of histopathological analysis after orchiectomies of transgender women. One case series found 5 germ cell neoplasms in 4 patients, out of 458 procedures, over 5.5 years [83]. An earlier summary of cases found 6 cases of malignant lesions out of 2555 patients, over 5 years [84], and a third study found 1 case of testicular cancer out of 722 [85]. In [83], the authors used the 5.5 years during which the orchiectomies occurred to calculate an annual incidence 26.5 times higher than those estimated for the general population by the National Cancer Institute. They hypothesized that this large increase in incidence might result from "long-term pretreatment with hormones or blockers" (they do not provide the amount of time each patient was on hormones).

3.7 Breast cancer

A recent systematic review and meta-analysis of the incidence of breast cancer among transgender women calculated a standardized incidence ratio (SIR) of 22.5 (95% CI 5.54–91.8) in comparison to non-TGNB men [86]. Excluding one study contributing to significant heterogeneity, the SIR compared to non-TGNB men increased to 40.7 (95% CI 26.2–63.1). (The Male Breast Cancer Pooling Project found a significant association of circulating estradiol levels among men with the incidence of breast cancer, with men in the highest quartile having an odds ratio of 2.47 (95% CI 1.10–5.58) compared to those in the lowest quartile [87].)

3.8 Adverse drug reaction reports

Adverse drug reactions (ADRs) in the US FDA Adverse Event Reporting System (FAERS) database for transgender women included "neoplasms (benign, malignant, and unspecified, including cysts and polyps)" [88]. In the French pharmacovigilance database, the principal adverse drug reaction for GAH therapy for transwomen was meningiomas, followed by cardiovascular events, with a median time to onset of 5.3 months [89].

The above studies are summarized in Table 1.

4 Some physiological effects of estrogen on the male brain

Estrogen also affects the male brain. Several small studies (8–14 patients) found estrogen use for 4 to at least 6 months was associated with an increase in ventricular volume and a decrease in brain volume [90–92]; other changes are described in Table 3. Similarly, in an experiment in male rats [93], pharmacologic doses of estradiol with or without cyproterone acetate (an anti-androgen) significantly reduced brain cortical volumes (in both hemispheres), increased fractional anisotropy, and increased glutamate concentration in the hippocampus, compared to controls; other increases were seen for estradiol alone (see Table 3). In the presence of the exogenous estrogen, water content was depleted within the astrocytes and the oligodendrocytes. This was associated with loss of cortical volume, reduction in the expected age-related decline in fractional anisotropy by MRI scanning, and the observed increased concentration of (glutamine for estradiol alone and) glutamate in the brain. These researchers had earlier observed similar changes from testosterone given to female rats [94]. The preservation of fractional anisotropy in the brains of the male rats treated with estrogen and cyproterone was unexpected given the findings in female rats after androgen enhancement. The clinical implications of these findings in humans are uncertain, other than providing some mechanistic support for the changes observed by MRI in brain structure volumes in both male and female humans given cross-sex hormones.

An association of estrogen and antiandrogens (19 patients, for 12 months) with reduced serum BDNF (Brain-Derived Neurotrophic Factor), thought to be associated with psychosocial "stress," was found [95]; this reduction would be reflected in lower levels of brain-tissue BDNF [96]. In [97], lower BDNF levels were found to be associated with an increased risk of developing major depressive disorder.

In addition, an association between major depression and reduced hippocampal (and frontal lobe and gray and white matter) volume has been seen in structural MRI scans of 34 inpatients with previous or current episodes of major depression relative to the same number of healthy controls. Smaller hippocampal white matter volumes were seen only among the patients, and lower hippocampal volumes were also correlated with poorer performance in cognition tests [98].

Increased symptoms of depression were associated with increased serum levels of estradiol for the 2244 men under—but not the 1681 men over—the age of 60 in the LIFE Adult Study [99] and with elevated depression and anxiety scores in 260 boys aged 11–17 [100].

Based on the summarized studies, a potential causal mechanism linking estrogen administration to observed brain changes in males involves estrogen-induced alterations in brain water content, specifically a depletion within astrocytes and oligodendrocytes. This cellular dehydration is associated with a loss of cortical volume and increased glutamate concentration in the hippocampus. Furthermore, the findings suggest that estrogen, particularly when combined with antiandrogens, may reduce serum BDNF levels, a neurotrophic factor linked to neuroplasticity and mood regulation. Lower BDNF has been associated with an increased risk of major depressive disorder and reduced hippocampal volume, changes also observed in individuals with depression. These interconnected findings—estrogen's impact on brain volume, neurotransmitter levels, and BDNF—offer a plausible biological pathway through which estrogen administration could contribute to structural brain changes and potentially influence the psychosocial outlook in males. Further studies to elucidate these mechanisms and their clinical implications are called for.

Gray matter damage is associated with memory loss, cognitive impairment, and motor movement issues [101], and an increase in ventricle size is associated with degenerative brain disease and gait [102], but causality is not understood.

Table 2 summarizes the above studies, while Table 3 summarizes the brain changes and the medical conditions associated with each particular brain change.

5 Discussion

This paper includes many reviews and observational studies of safety signals ranging from cohort control studies to case studies. Even though the latter are often criticized as weak evidence for treatment benefits, they are valuable for identifying possible harms, especially rare or severe adverse effects that may not be detected or reported in limited-duration clinical trials. Important safety signals sometimes only become apparent through case series, individual case reports, or post-marketing surveillance, rather than randomized controlled trials that focus more on detection of benefits rather than (perhaps) somewhat rarer harms (which might only become apparent only over the longer term). Even if causality

Table 1 Associated physiological harms

Study	Study type	Associations
Schneider et al. [38]	Case series 108 patients obtaining surgery	24% of patients had spermatogenesis
Schneider et al. [39]	Review 11 papers	"Highly variable outcomes from qualitatively normal spermatogenesis and undisturbed Leydig/Sertoli cell morphology to full testicular regression with severe cellular damage and hyalinization." (p. 873)
De Roo et al. [40]	Systematic review 46 studies (30 histopathology, 16 fertility preservation), including three animal studies; with and without control groups	Atrophic testes having "smaller seminiferous tubules with heavy hyalinization and fibrosis… Oestrogen and anti-androgen treatment resulted in higher proportions of sperm abnormalities (low total sperm count, low sperm concentration, poor sperm motility) or azoospermia; however, some of these effects seem to be reversible upon cessation"
Cheng et al. [41]	Review	A fraction of patients in different studies had preserved spermatogenesis (24% in Schneider et al. [38], above), while others had testicular atrophy, hyalinization, fibrosis, cessation of spermatogenesis
Vereecke et al. [42]	Prospective cohort study 97 patients	"Adequate hormonal therapy (HT) leads to complete suppression of spermatogenesis in most TW, if serum testosterone levels within female reference ranges are obtained"
Adeleye et al. [43]	Retrospective cohort study 28 patients, 3 groups compared: no hormones, after discontinuation of hormones, while receiving hormones	Sperm parameters (no hormones, after discontinuation, while receiving): Concentration (63.6 M/mL, 39.0 M/mL, 2.4 M/mL), ($P < .01$) Percent motility (51.5%, 34.3%, 15.6%), ($P < .01$) Total motile count (63.2 M,39.1 M, 0.2 M), ($P < .01$)
Riva-Morales et al. [46]	Cohort study Histological and biochemical analysis of 63 orchiectomy specimens	Testicular atrophy, decreased spermatogenesis, reduced mean tubule diameter with basement membrane thickening, maturation arrest, and aspermatogenesis 65% showed germ cell nucleomegaly with cytological atypia mimicking germ cell neoplasia in situ
Matoso et al. [47]	Cohort study 99 orchiectomies from 50 patients	13% testes hypertrophic, "decreased diameter of seminiferous tubules and expansion of the interstitium [~80%], (2) marked hypoplasia of germ cells [80%], (3) rare cytomegaly [26%], (4) Complete absence of [53%] or markedly reduced [32%] Leydig cells, and (5) epididymal hyperplasia [20%]"
Marins et al. [48]	Cross-sectional study 86 patients	"Duration of hormone treatment is associated with testicular atrophy and spermatogenesis arrest"
Glintborg et al. [49]	Narrative review, CVD and diabetes risk among transgender men and women	Increased risk of CVD among those on feminizing hormone therapy Higher fat mass and insulin resistance among those on feminizing hormone therapy
van Zijverden et al. [50]	Meta-analysis and Systematic review, 10 studies of 15,781 transgender women; comparing transgender women to non-transgender men	Stroke incidence 1.3 (95% confidence interval [CI] 1.0–1.8) times higher than in non-TGNB men (11,268 TW included) VTE incidence 2.2 (95% CI 1.1–4.5) times higher (9751 TW included), did not look at long-term difference Death due to any CVD in 1.5% (59/3965) of trans women, relative risk of 1.5 (95% CI 1.1–2.0) to non-TGNB men

Table 1 (continued)

Study	Study type	Associations
Irwig [51]	Narrative review	Risk of VTE increases "over fivefold," with transdermal estrogen likely carrying a lower risk than oral estrogen SMR of 1.64 (95% CI 1.43–1.87) for ischemic heart disease SMR of 2.11 (95% CI 1.32–3.21) for those aged 40–64 for fatal stroke Lowering testosterone in TW decreases hemoglobin Possible increase in triglycerides and systolic blood pressure
Franco-Moreno et al. [52]	Systematic review 21 papers	Occurrence of thrombosis was higher in TW than non-TGNB men (OR: 2.23; 95%CI 1.93–2.57; P < .001)
Bøgehave et al. [53]	Cohort study 270 TW older than 17; thrombin generation (TG) variables—endogenous thrombin potential (ETP) and peak TG—measured at baseline and after 12 months	ETP and peak TG increased after oral and transdermal estradiol (P < .001) with larger increases after oral estradiol (ΔETP: 113 nmol/L × min, P = .011; Δpeak TG: 28 nmol/L, P = .009)
Nota et al. [54]	Cohort-control study Dutch, 2517 TW, median age 30 years	4.6 × VTE relative to non-TG men, median 6 year (average 9 year) follow-up time, (95% CI 3.59–5.69) 1.8 × stroke relative to non-TG men, median 6 year (average 9 year) follow-up time, (95% CI 1.23–2.56)
Getahun et al. [55]	Cohort-control study US, 853 TW	50% more VTE < 2 years relative to non-TG men 5.1 × higher VTE 2 + years (HR 95% CI 2.1–12.6) 9.9 × stroke 6 + years (HR 95% CI 3.0–33.1)
Andzembe et al. [61]	Case study	Branch retinal vein occlusion (BRVO) after transdermal estrogen, "estrogen increases cardiovascular risk when used in hormone replacement therapy, RVO [retinal vein occlusion] is a complication that must be taken into account…especially in transgender women who are more at risk."
Karalexi et al. [62]	Systematic review and meta-analysis, 8 studies involving a total of 234 males (162 on hormones), average ages ranging from 26.7 to 42.5, small sample size: 10–31 patients receiving estrogen, time on hormones unspecified	No detrimental change seen in scores examined
van Heesewijk et al. [63]	Case–control study 73 TW (56–84 years old), an average of 28.5 years on hormones	Lower scores—information-processing speed (tested using a coding task) and episodic memory (tested using a 15-word immediate and delayed recall test)
*Lambrou et al. [65]	Cross-sectional study 408 TGNB in Behavioral Risk Factor Surveillance System (BFRSS)	37% higher prevalence of subjective cognitive decline as compared to their non-transgender counterparts (results not broken down by gender or hormone use)
de Blok et al. [66]	Retrospective population cohort study, 2927 TW from gender identity clinic of Amsterdam University Medical Centre in the Netherlands (90% of those in country)	SMR was higher compared to men in the general population (SMR 1.8, 95% CI 1.6–2.0). The major causes of death included cardiovascular disease (21%), cancer (32%), infection-related disease (5%), and suicide (7.5%)
Ruuska et al. [67]	Cohort study Finnish record search, 2083 adolescents (age < 23) who contacted specialised gender identity services 1996–2019 compared to 16,643 matched controls	"Main predictor of mortality in this population is psychiatric morbidity, and medical gender reassignment does not have an impact on suicide risk"
Asscheman et al. [68]	Cohort study Baseline and follow-up data from patients in clinic (966 MTF), median follow-up of 18.5 years; appears to be subset of [54]	51% higher mortality than the general population, elevated lung and hematological (but not total) cancer mortality, 3 × increased risk of death from CVE for current use of ethinyl estradiol

Table 1 (continued)

Study	Study type	Associations
*Hughes et al. [69]	Cohort study American private insurance data	MTF die much earlier than non-TGNB men, starting around age 30 (results not broken down by hormone use), reaching 19.5% probability of dying before 60 compared to 7.7% for a non-TGNB man (Hughes et al. [69], including online Appendix in [69])
*Jackson et al. [70]	Population cohort study 1951 TW from longitudinal study using Clinical Practice Research Datalink GOLD and Aurum databases	Mortality rate ratio, MRR, of 1.34 (95% CI 1.06–1.68) relative to non-TGNB men, and 1.60 (95% CI 1.27–2.01) with non-TGNB women
*Dragon et al. [71]	Cross-sectional study 7454 TG and 39,136,229 non-TG Medicare beneficiaries	Higher incidence of chronic conditions Higher observed rates of potentially disabling mental health and neurological/pain conditions, also obesity, nonhepatitis liver disorders (results not broken down by hormone use)
Salgado et al. [73]	Scoping review, 11 case reports	Case studies of rheumatoid arthritis (1), ankylosing spondylitis (1), systemic lupus erythematosus (SLE, rare in men, 4), skin lupus erythematosus (1), and systemic sclerosis (4)
Arneson and Varga [74]	Case study	Scleroderma renal crisis after starting estrogen
*Pakpoor et al. [75]	Cohort study Retrospective, of (English) Hospital Episode Statistics (HES) from 1999 through 2012, 1157 natal men with gender identity disorder, matched to reference cohort from rest of population (no MS at or before admission)	Adjusted rate ratio of multiple sclerosis of 6.63 ([95% CI 1.81–17.01, p = 0.0002). Result not broken down by hormone use
Spanos et al. [76]	Review 16 studies of TW with different measurements, follow up 4 months to 8 years (most 1 or 2 years)	Decreases lean mass, increases fat mass, and may worsen insulin resistance: 5 studies showed increased insulin resistance, 3 showed no change
Colizzi et al. [77]	Cohort study 79 participants, 2 years, included in Spanos et al. [76]	Increase in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) by 72% in 12 months, by 9% more (compared to baseline) in next 12 months
Panday et al. [78]	Review 11 studies, including Spanos et al. [76]	GAH increased BMI and insulin resistance in transgender population compared to controls
Chaudhry et al. [79]	Case study	Hypertriglyceridemia-induced acute pancreatitis
Freier et al. [80]	Case study	Development of gallstone pancreatitis
*Christensen et al. [82]	Retrospective cohort study US Veterans Health Administration records, July 2017 through December 2022	Thyroid cancer in 0.34% (34/9988 TW) compared to 0.64% of non-TGNB women and 0.19% of non-TGNB men. 11/34 were taking estrogen at the time of diagnosis of thyroid cancer
*Shanker et al. [83]	Case series Pathology outcomes for 458 orchiectomies during 5.5 years, time on hormones unspecified	Found 5 germ cell neoplasms in 4 patients over 5.5 years, calculated incidence rate per year of 159/100,000, 26.5 × the National Cancer Institute's (NCI) average incidence rate of 6.0/100,000
Bonapace-Potvin et al. [84]	Case series Pathology outcomes for 2555 orchiectomies (plus vaginoplasties) in 5 years	Found 6 cases of malignant lesions of orchiectomies over 5 years, converts to annual rate 47/100,000, 8 × higher than NCI's average incidence rate of 6/100,000. Patients with positive pathology were on hormones for an average of 3.5 years

Table 1 (continued)

Study	Study type	Associations
de Nie et al. [85]	Retrospective cohort study, Dutch nationwide Case series, pathology outcomes for 722 orchiectomies, time on hormones unspecified Also, 1112 no orchiectomies, including 523 TW follow-up > 5 years on hormones, median 8.9 (6.4–13.9 years interquartile range)	1 case of testicular cancer among the 722 with orchiectomies, over unspecified time period 2 cases for those not among orchiectomies and < 5 years (SIR 0.8, 95% confidence interval 0.1–2.8) For 523 with follow-up > 5 years, no testicular cancer observed
Corso et al. [86]	Systematic review and meta-analysis (3 cohort studies and 16 case reports among TW)	SIR of breast cancer 22.5 (95% CI 5.54–91.8) compared to non-TGNB men. Excluding one study contributing to significant heterogeneity, the SIR compared to non-TGNB men increased to 40.7 (95% CI 26.2–63.1)
Gomez-Lumbreras and Villa-Zapata [88]	Case series Analysis of adverse drug reactions related to GAH reported in the US FDA Adverse Event Reporting System (FAERS)	More than half of the reports associated with transgender hormone therapy (53.6%) classified as serious ADRs, with "meningioma" and "prolactin-producing pituitary tumor" being the two most used "Preferred Terms". Included "neoplasms (benign, malignant, and unspecified, including cysts and polyps)." Mean age of patients 33.3 years
Yelehe et al. [89]	Case series Analysis of adverse drug reactions related to GAH reported in the French pharmacovigilance database	77% of the cases were associated with estrogens (primarily in association with progestin or cyproterone acetate), 68% involved antiandrogens (mainly cyproterone acetate). Principal adverse drug reactions involved meningiomas, followed by CVE, with a median time to onset of 5.3 months

*Signifies that it is not established that all transgender patients in the particular study are on hormones

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Table 2 Brain studies

Authors	Procedure
Pol et al. [90] Case–control study	8 MTF + age-matched controls, MTF measured before hormones, after 4 months, and before surgery
Seiger et al. [91] Prospective longitudinal observational study	14 MTF + controls: MRI assessments before starting and after at least 4 months of estradiol and antiandrogens, two MRI assessments each for 14 female and 12 male untreated controls
Zubiaurre-Elorza et al. [92] Prospective longitudinal observational study	14 MTF, no controls, before and after at least 6 months of estrogen and anti-androgens
Gómez et al. [93] Experimental animal study	Thirty adult male rats, randomized to either 1. receive pharmacological doses of estradiol (E_2) 2. receive estradiol and cyproterone acetate (E_2 + CA, a common anti-androgen in feminization therapy for transgender women) 3. be controls Structural MRI and Diffusion Tensor Imaging on Days 1, 15, and 30
Fuss et al. [95] Prospective longitudinal observational study	19 MTF, no controls, after 12 months

Table 3 Observed brain changes with exogenous estrogen plus anti-androgen, along with medical conditions that have been associated with each particular brain change

Effect	Study/studies
Shrink different parts of the brain	Rats: decreased brain cortical volumes, both hemispheres [93] 8 MTF + controls, hypothalamus decrease [90] 14 MTF + controls, statistically significant decrease in right hippocampal volume relative to controls, reflected in ventricular structure increase; changes of gray matter correlated with progesterone decrease [91] 14 MTF, no control, decrease in brain cortical thickness and subcortical volumetric measures [92]
Increase glutamate concentration in the hippocampus	Rats, E_2 + CA group [93] Also an increased concentration of glutamate and glutamine in the hippocampus, the hypothalamus, the parietal cortex, and the frontal lobe in the E_2 group [93]
Reduce water content in astrocytes and oligodendrocytes	Rats [93]
Reduce gray matter	14 MTF + controls, correlated with progesterone decrease [91]
Increase in relative fractional anisotropy relative to controls	Rats [93]
Increase ventricle volume	8 MTF + controls [90] 14 MTF + controls [91] 14 MTF, no controls [92]
Lowered BDNF	19 MTF, no controls [95]

cannot (perhaps yet) be firmly established, adverse effects must be reported to communicate potential risks to clinicians and patients, as part of a full account of patient experiences, and, as we elaborate below, to motivate future investigation. In addition, medical decision-making tends to prioritize avoiding harm over achieving benefit, particularly when harms are severe and benefits are modest. This risk aversion means that even weak evidence of harm, such as from case reports, is taken seriously in clinical practice. Cataloguing potential harms is thus a critical part of evaluating treatments, and as noted above, for gender-affirming hormone therapy for natal males these harms are occurring alongside an inability to

identify those likely to benefit from these interventions [20].[2] This focus on harms should be seen as a necessary component of patient safety and informed clinical decision-making.

In addition to alerting clinicians and patients to open questions and possible concerns, the aforementioned safety signals, many of which highlight life-altering and potentially life-threatening adverse outcomes, necessitate rigorous further investigation. For instance, current clinical understanding, reflected in guidelines such as those from WPATH [2], recognizes that long-term, supraphysiologic estrogen use in transgender women carries clinically significant risks. However, the precise nature, frequency, and contributing factors for these acknowledged harms are not yet well-defined. As discussed here, significant concern exists that such long-term, supraphysiologic exposure to estrogen may exacerbate previously identified associated harms, potentially increasing the severity or frequency of outcomes like acute cardiovascular events and cognitive decline. The lack of systematic, long-term data extends even to anticipated physiological changes; for instance, while lifelong sterility is generally expected after a few years, to our knowledge, comprehensive longitudinal outcomes have not been reported. Compounding the uncertainty surrounding the well-acknowledged risks, the emerging evidence reviewed in this paper points towards additional, less-understood and less-investigated potential risks. Consequently, both patients and healthcare providers are deprived of clinically crucial information necessary for effective risk assessment and management.

Given the wide range and severity of safety signals discussed here, valuable next steps could include a comprehensive systematic literature review of reported adverse outcomes for feminizing estrogen in males and prioritization of tracking and reporting of adverse outcomes in studies and systematic reviews. Systematic reviews often fail to explore harm [103–105] (and some findings regarding various harms [28] are currently unpublished). As mentioned above, there is also a dearth of studies that track patients over long periods to ascertain long-term risks, and most individual studies suffer from uncontrolled confounding, which makes it difficult to isolate the effects of hormone therapy [18]. The outcomes described here may aid in designing future study outcome and inclusion specifications, such as follow-up time, and/or use of other medications (e.g., anti-androgens), comorbidities, or other confounders. Further exploration of the data in hand may be valuable. For example, as with [55] above, the data sets of [66, 69] may also have finer-grained information, as well as countries with extensive centralized medical records, such as Sweden. There are also proposals for research to support better estimates of cardiovascular disease risk in the TGNB population [50]. Better-designed and more informative studies, supplemented by systematic reviews to assess their reliability, will lead to more accurate information about medical risks supporting ethical, informed consent and, more broadly, the clinical, scientific, and ethical standards outlined by ESCAP [1].

6 Directions for future work

The term GAHT encompasses medical interventions for both natal males and natal females. However, the physiologic and mental effects of and adverse reactions to these hormonal interventions can vary widely depending on sex, age, prior affirming medical interventions, recommended supraphysiologic dosing, duration of intervention, interactions with concurrent treatments, and potentially additional unknown criteria. As the discussion on the emerging safety signals for the treatment of natal males demonstrates, the range of signals alone is vast, potentially running against the length limitations of a single journal submission. The emerging safety signals for hormonal treatment of natal females for gender dysphoria deserve a separate discussion of their own in a future submission.

The poorly understood but significant rise in GD diagnoses among young people in recent decades necessitates prioritizing adequate long-term follow-up studies. For instance, England experienced a more than 50-fold increase in GD diagnoses among children and adolescents between 2011 and 2021 [33], yet there continues to be very little long-term follow-up data. At the same time, "[y]oung people's sense of identity is not always fixed and may evolve over time" ([4], p. 21), and their perceptions of gender and gender dysphoria are also subject to change [106]. Not surprisingly, a subset of these patients discontinue treatment due to a multitude of reasons, and there has been a rise in the cessation of gender-affirming therapies among young individuals [4, 107, 108]. This significant rise in

[2] Notably, that same study recorded two suicides among participants receiving hormone therapy within the first 12 months, underscoring the gravity of potential adverse outcomes.

medical transition and subsequent detransition (sometimes called "retransition") also demands long-term follow-up studies [109]. There is a dearth of research addressing detransition, including but not limited to rates of detransition [110, 111] and medical and psychological short- and long-term sequelae of detransitioning for both sexes. Given the increasing reports of harm and regret, and the lack of research demonstrating the safety and efficacy of current treatment options for this vulnerable population, it is imperative that future research endeavors prioritize the identification of safe and effective interventions. Furthermore, it is essential to enhance our understanding of and ability to communicate potential risks, including life-altering and permanent adverse effects, to patients and families. This will enable informed decision-making and minimize harm.

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