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5 UNSOLICITED REVIEW

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A systematic review of antiandrogens and feminization in transgender women

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Abstract

Antiandrogens are frequently used with estradiol in transgender women seeking feminization. Antiandrogens act by various mechanisms to decrease the production or effects of testosterone, but it is unclear which antiandrogen is most effective at feminization. A systematic review was performed using PRISMA guidelines. We searched online databases (Medline, Embase and PsycINFO) and references of relevant articles for studies of antiandrogens in transgender women aged 16+ years to achieve feminization (namely changes in breast size, body composition, facial or body hair) or changes in serum total testosterone concentration when compared to placebo, estradiol alone or an alternative antiandrogen. Four studies fulfilled eligibility criteria and were included in a narrative review. The addition of cyproterone acetate, leuprolide and medroxyprogesterone acetate may be more effective than spironolactone or estradiol alone at suppressing the serum total testosterone concentration. Body composition changes appear similar in transgender women treated with estradiol and additional cyproterone acetate or leuprolide. No eligible studies adequately evaluated the effects of antiandrogens on breast development or facial and body hair reduction. It remains unclear which antiandrogen is most effective at achieving feminization. Cyproterone acetate, medroxyprogesterone acetate and leuprolide may be more effective than spironolactone at suppressing the serum total testosterone concentration. However, due to spironolactone's antagonism of the androgen receptor, it is unclear whether this results in clinically meaningful differences in feminization. Further research with clinically meaningful endpoints is needed to optimize the use of antiandrogens in transgender women.

KEYWORDS
antiandrogen, cyproterone acetate, feminization, spironolactone, testosterone, transgender

1 | INTRODUCTION

Trans, gender diverse and nonbinary individuals desiring feminization (herein referred to as transgender women) frequently seek medical care to achieve physical changes such as breast development, body fat redistribution and a reduction in facial and body hair.[1] Given oestrogen monotherapy at physiological doses is not typically able to suppress serum total testosterone concentrations to the normal female range,[2-4] treatment guidelines recommend the addition of an antiandrogen to assist with feminization.[1,5,6]

For the purposes of this review, antiandrogens are defined as medications other than estradiol which are used to decrease the synthesis of or actions of androgens. Broadly speaking, mechanisms involve suppression of gonadotrophin secretion, inhibition of key enzymes in androgen biosynthesis and antagonism of the androgen receptor. This expanded definition includes gonadotrophin-releasing

hormone (GnRH) analogues, progestogens, 5α-reductase inhibitors and androgen receptor antagonists.

The prescription of antiandrogens is highly variable throughout the world, reflecting differences in access and the cost of medications, prescriber familiarity and preference as well as the absence of rigorous data. In the United States, spironolactone is commonly prescribed as cyproterone acetate (CPA) is not licensed for use whereas CPA appears to be favoured in many European countries and forms standard care as part of the European Network for the Investigation of Gender Incongruence (ENIGI) treatment protocol.[6] In the United Kingdom, the high cost of GnRH analogues is heavily subsidized, facilitating first-line use in combination with estradiol.[7] In Australia, both spironolactone and CPA are subsidized by the Pharmaceutical Benefits Scheme (PBS), while the use of GnRH analogues is not PBS subsidized for transgender people and is funded instead by individual hospitals for the purpose of puberty suppression.

The mechanisms of action of the available antiandrogen agents are summarized in Table 1. Androgen receptor antagonists include the steroid medications spironolactone and CPA, and nonsteroid medications such as bicalutamide. While generally used for its mineralocorticoid antagonist properties, spironolactone exerts antiandrogen effects which have been exploited for the purposes of feminization since the 1980s.[4] Spironolactone is a moderate androgen receptor antagonist,[8,9] which also partially inhibits 17α-hydroxylase/17,20 lyase, enzymes involved in testosterone synthesis.[10] Interestingly, even at high doses spironolactone treatment was not associated with a significant reduction in serum total testosterone concentration and actually caused a transient increase in luteinizing hormone in a small pharmacodynamic study of five healthy men.[11] However, another study demonstrated that the administration of canrenone, a metabolite of spironolactone, at high doses caused a significant reduction in the total serum testosterone concentration[12] and the addition of spironolactone to estradiol appears to assist with suppression of testosterone to female concentrations in transgender women.[4] An observed increase in serum estradiol and estrone concentrations[13] as well as interaction with the oestrogen receptor with spironolactone therapy[14] may also contribute to feminization. Due to structural similarity to progesterone, spironolactone also possesses partial progesterone receptor agonist activity,[9] though the relevance of this to feminization is unclear. In comparison, CPA has also been used as part of feminizing therapy since the 1980s and is a potent progestogen which exerts negative feedback on the hypothalamic-pituitary-gonadal axis to decrease gonadotrophin secretion and testosterone levels as well as moderate androgen receptor antagonism.[15]

Nonsteroid androgen receptor antagonists such as bicalutamide are highly potent and as monotherapy does not cause a reduction in gonadotrophins or testosterone levels in contrast to CPA. Aromatization of testosterone to estradiol is hypothesized to contribute to increased feminization which was observed in transgender girls treated with bicalutamide without estradiol.[16] Other antiandrogens include GnRH analogues and progestogens which suppress the hypothalamic-pituitary-gonadal axis to decrease testosterone levels and 5α-reductase inhibitors, which decrease the conversion of testosterone to the more potent androgen dihydrotestosterone.

While there are numerous antiandrogens available to augment estradiol therapy in transgender women, it remains unclear which antiandrogen is the most effective at inducing changes of feminization including breast growth, body fat redistribution and reduction of facial and body hair. As such, the aim of this systematic review was to synthesize available evidence to determine the comparative efficacy of antiandrogens to cause clinically meaningful feminization—the ultimate objective of feminizing hormone

TABLE 1 Antiandrogen mechanisms of action

Antiandrogen drugs	AR antagonist	PR agonist	ER agonist	Suppression of HPG axis
Spironolactone	Yes (weak)	Yes (weak)[a]	Yes (weak)[a]	No[b]
Cyproterone acetate	Yes (moderate)	Yes (strong)	No	Yes
Nonsteroid antiandrogens (eg bicalutamide)	Yes (strong)	No	No	No[b]
GnRH analogues (eg leuprolide and triptorelin)	No	No	No	Yes
5—alpha reductase inhibitors (eg finasteride)	No	No	No	No[b]

Abbreviations: AR, androgen receptor, ER, oestrogen receptor, HPG axis, hypothalamic-pituitary-gonadal axis, GnRH, gonadotrophin-releasing hormone, PR, progesterone receptor.

[a]Clinical significance uncertain.

[b]When used as monotherapy, reduced stimulation of the androgen receptor would be expected to stimulate the HPG axis to increase testosterone production. When combined with estradiol at sufficient doses, suppression of the HPG axis may occur resulting in decreased testosterone levels.

therapy. While the comparative safety of antiandrogen medications is also an important consideration, it is not the focus of this review.

2 | METHODS

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting guidelines were used in the development of this systematic review.[17]

2.1 | Eligibility criteria

2.1.1 | Study types

Given the paucity of randomized controlled trials evaluating the efficacy of gender-affirming hormone therapy, we considered the following types of studies for inclusion if published in English in a peer-reviewed journal: randomized controlled trials, prospective nonrandomized cohort studies, retrospective cohort studies, retrospective case-control studies.

2.1.2 | Participants

We included studies with transgender women aged 16 years and over, the age at which gender-affirming hormone therapy is commonly commenced.

2.1.3 | Interventions

Antiandrogen medications including steroid and nonsteroid androgen receptor antagonists, 5α-reductase inhibitors, progestogens and GnRH analogues.

2.1.4 | Comparators

Comparators including placebo, estradiol therapy alone or an alternative antiandrogen. We chose not to include observational studies of estradiol with an antiandrogen in a single treatment cohort due to the inability to distinguish whether the observed effects were related to estradiol or antiandrogen therapy.

2.1.5 | Outcomes

Clinical outcomes of interest included clinical features of feminization (breast growth, body composition, suppression of facial and body hair). Serum total testosterone concentration was also examined as a surrogate marker of feminization.

2.2 | Information sources & search strategy

A search of online databases (MEDLINE, Embase and PsycINFO) was performed independently by the first two authors using the Ovid platform including records from inception to 16 April 2020. The search strategy used was as follows: 'transgender' OR 'transsexualism' OR 'gender dysphoria' OR 'gender identity' OR 'transfeminine' OR 'transfemale' OR 'MtF' OR 'trans wom*' OR 'transwom*' AND 'androgen antagonist' OR 'antiandrogen' OR 'spironolactone' OR 'cyproterone' OR 'bicalutamide' OR 'flutamide' OR 'finasteride' OR 'dutasteride' OR 'progest*' OR 'gonadorelin' AND 'femini*' OR 'body composition' OR 'hair' OR 'breast' OR 'testosterone'. Additional records were identified from the reference lists of relevant articles. Gray literature sources were not searched.

2.3 | Study selection

Following the removal of duplicates, two authors (LMA and BJN) independently screened the titles and abstracts of records for relevance against eligibility criteria. Review articles, conference abstracts, case reports, articles not published in English and irrelevant articles were removed. The full text of remaining articles was assessed for eligibility, with data recorded including author, year of publication, study design, country of origin, study population, intervention, comparator and outcomes measured. Authors of studies were not contacted for additional unpublished data. Any discrepancies between the two review authors were resolved by consensus or arbitration by the senior author (ASC) in the event of disagreement.

3 | RESULTS

3.1 | Search results

The literature search yielded 886 articles and 20 additional articles were identified from the reference of relevant articles. After duplicates were removed, 680 records were subjected to title and abstract screening. The full text of the remaining 32 records was reviewed and four articles fulfilled eligibility criteria for inclusion. See Figure 1 for full details of the review process.

3.2 | Included studies

There were four studies deemed eligible for inclusion. All included studies were retrospective analyses of transgender women treated with an oestrogen (estradiol or conjugated equine oestrogens) with or without an antiandrogen. Table 2 details the characteristics of the included studies. Given the small number and heterogeneity of studies, meta-analysis was not performed and a narrative summary is provided.

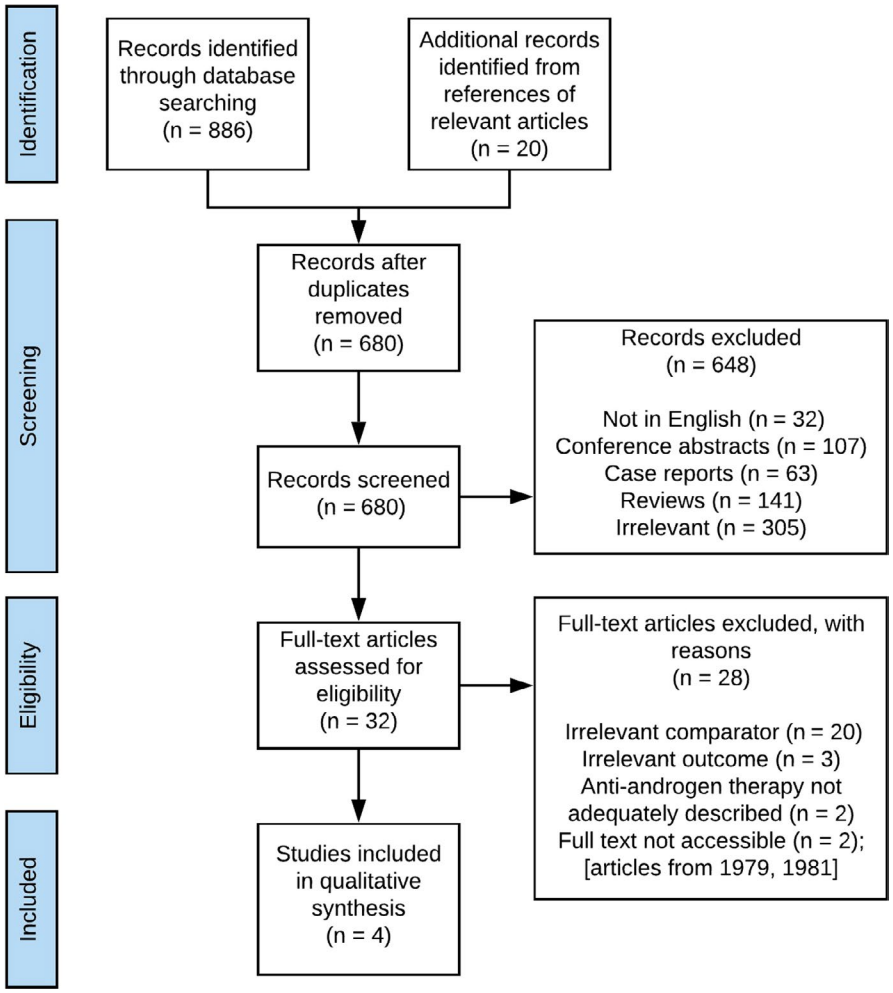

FIGURE 1 Flow diagram detailing systematic review process including identification and screening of records, assessment for eligibility and inclusion in review [Colour figure can be viewed at wileyonlinelibrary.com]

3.3 | Serum total testosterone concentration

Serum total testosterone concentration was the most frequently reported outcome of interest in included studies and is commonly used as a surrogate for the efficacy of feminizing therapy. Gava et al[18] compared the efficacy of GnRH analogues or CPA in addition to estradiol in a retrospective study. Forty transgender women were randomized to treatment with leuprolide 3.75 mg intramuscular injection monthly or CPA 50 mg daily, in addition to standard estradiol therapy for 12 months. The serum total testosterone concentration decreased from 16.3 ± 8.3 nmol/L at baseline to 0.7 ± 1.0 nmol/L at 12 months in the CPA group ($P < .05$) and from 22.2 ± 7.6 nmol/L at baseline to 0.7 ± 0.3 nmol/L at 12 months in the leuprolide group ($P < .05$), representing significant changes from baseline but with no significant difference between groups.

The addition of medroxyprogesterone (MPA) to estradiol was explored in a retrospective study performed by Jain et al[19] Data were recorded from 290 follow-up visits of 92 transgender women treated with estradiol and spironolactone 100-200 mg, with or without MPA (5-10 mg oral daily or 150 mg intramuscular injection 3 monthly). Serum total testosterone concentration was significantly lower in the MPA group (79 ± 18 ng/dL (2.74 ± 0.62 nmol/L)) than the non-MPA group (215 ± 29 ng/dL (7.45 ± 1.01 nmol/L)) ($P < .001$).

A retrospective analysis compared the serum testosterone concentration in 80 transgender women treated with estradiol alone (n = 21), estradiol plus spironolactone (median dose 100 mg daily) (n = 38) or estradiol plus CPA (median dose 50 mg daily) (n = 21).[3] This showed a significantly lower median serum total testosterone concentration in those treated with CPA (0.8 nmol/L), compared to spironolactone (2.0 nmol/L) and estradiol alone (10.5 nmol/L) ($P = .005$ after adjustment for serum estradiol concentration, estradiol dose, spironolactone dose, CPA dose and age). In contrast, Cunha et al[20] observed a significant reduction in serum total testosterone concentrations at 6 months compared to baseline in a retrospective analysis of 51 transgender women treated with conjugated equine oestrogens (CEE) alone or with CPA 50-100 mg daily, but no significant between-group difference (median serum total testosterone concentration at 6 months 21 ng/dL (0.73 nmol/L) in the CPA group versus 18.0 ng/dL (0.62 nmol/L) in the CEE alone group, $P = .217$).

3.4 | Body fat redistribution

Gava et al[18] compared body composition, assessed by anthropometry and dual X-ray absorptiometry (DXA), in those treated with estradiol plus CPA versus estradiol plus leuprolide over a 12 month

TABLE 2 Characteristics of included studies

Author	Sample size	Age (mean ± SD)	Intervention	Duration of intervention	Clinical outcomes	Change in serum total testosterone concentration
Gava et al (2016)[18]	40	CPA group 32.9 ± 9.4 Leu group 29.4 ± 10.2	CPA 50 mg daily + E2 vs Leu 3.75 mg monthly + E2	12 mo	**Body composition**: No significant between-group difference Total body fat increased at 12 months in both the CPA group (19.3 ± 4.7 kg vs 14.9 ± 5.6 kg at baseline, $P < .05$) and the leuprolide group (19.9 ± 6.8 kg vs 15.2 ± 5.6 kg at baseline, $P < .05$) but there was no significant between-group difference. Lean mass decreased in both the CPA group (49.9 ± 7.8 kg at 12 months vs 51.7 ± 8.3 kg at baseline, $P < .05$) and the leuprolide group (49.8 ± 6.7 kg at 12 months vs 50.2 ± 7.0 kg at baseline, $P < .05$), but no significant between-group difference	No significant between-group difference Testosterone decreased from 16.3 ± 8.3 nmol/L at baseline to 0.7 ± 1.0 nmol/L at 12 mo in the CPA group ($P < .05$) and from 22.2 ± 7.6 nmol/L at baseline to 0.7 ± 0.3 nmol/L at 12 mo in the leuprolide group ($P < .05$), representing significant changes from baseline but with no significant difference between groups
Cunha et al (2018)[20]	51	38.3 ± 7.4	CPA 50-100 mg + CEE vs CEE alone	6 mo	Nil relevant	No significant between-group difference Testosterone was 21 ng/dL (0.73 nmol/L) in the CPA group and 18.0 ng/dL (0.62 nmol/L) in the CEE alone group, with no significant between-group difference ($P = .217$)
Jain et al (2019)[19]	92	31.0 ± 7.1	E2 + SPL 100-200 mg + MPA 5-10 mg daily or MPA 150 mg IM 3 monthly vs E2 + SPL 100-200 mg	Variable	**Breast growth**: 26 of 39 participants taking MPA self-reported improvement in breast development, with no comparison to those not taking MPA **Facial and body hair**: 11 of 39 participants taking MPA self-reported a decrease in facial and body hair, with no comparison to those not taking MPA	Testosterone was significantly lower in the MPA group (79 ± 18 ng/dL (2.74 ± 0.62 nmol/L)) than the non-MPA group (215 ± 29 ng/dL (7.45 ± 1.01 nmol/L)) ($P < .001$)
Angus et al (2019)[3]	80	27	CPA 25-50 mg + E2 vs SPL 87.5-200 mg + E2 vs E2 alone	Variable	Nil relevant	Testosterone was significantly lower in the CPA group (0.8 nmol/L) than the spironolactone group (2.0 nmol/L) and estradiol alone group (10.5 nmol/L) ($P = .005$)

Abbreviations: CEE, conjugated equine oestrogens; CPA, cyproterone acetate, E2, estradiol; Leu, leuprolide; MPA, medroxyprogesterone acetate; SPL, spironolactone.

period. Notably, there was a significant increase in total body fat at 12 months in both the CPA group (19.3 ± 4.7 kg vs 14.9 ± 5.6 kg at baseline, $P < .05$) and the leuprolide group (19.9 ± 6.8 kg vs 15.2 ± 5.6 kg at baseline, $P < .05$) but no significant between-group difference. Additionally, there was a significant decrease in lean mass in both the CPA group (49.9 ± 7.8 kg at 12 months vs 51.7 ± 8.3 kg at baseline, $P < .05$) and the leuprolide group (49.8 ± 6.7 kg at 12 months vs 50.2 ± 7.0 kg at baseline, $P < .05$), but no significant between-group difference. There was no significant change in total body weight or waist-to-hip ratio throughout the study period.

3.5 | Breast development

Limited studies have been performed to systematically examine breast development in transgender women, and none have provided a comparison of different antiandrogens.

3.6 | Facial and body hair reduction

Limited studies have been performed to systematically examine reductions in facial and body hair in transgender women and none have provided a comparison of different antiandrogens.

4 | DISCUSSION

4.1 | Summary of evidence

Despite antiandrogens being prescribed to most transgender women, there is a profound lack of research to guide choice of therapy. No available studies assessed breast development or reduction in facial and body hair in a way that allows meaningful comparison of different antiandrogens. There was one study comparing body composition changes, which found no difference in body composition between GnRH analogues and CPA. Due to difficulty in measuring feminization, there is a reliance on the total testosterone concentration as a surrogate marker and evidence to date suggests that CPA, GnRH analogues and MPA are more effective than spironolactone at suppressing testosterone. However, serum total testosterone is an imperfect marker of treatment given androgen receptor antagonism is the predominant mechanism of action for many antiandrogens.

4.2 | Serum total testosterone concentration

Serum total testosterone concentration is frequently used as a surrogate marker of feminizing therapy and may be used for the titration of medication. However, there is a lack of data to support a clear relationship between suppression of serum total testosterone concentration and improved clinical feminization, especially given some antiandrogens work predominantly via antagonism of the androgen receptor rather than by decreasing testosterone levels. Indeed, use of nonsteroid androgen receptor antagonists (for example, bicalutamide) may cause feminization with an increase in total testosterone concentrations due to potent androgen receptor antagonism without negative feedback of the hypothalamic-pituitary-gonadal axis.[16] In terms of serum total testosterone concentration suppression, the included four studies in suggest that CPA, GnRH analogues and progestins may be more effective at suppressing serum total testosterone concentrations than spironolactone when combined with an oestrogen. The lack of between-group difference found by Cunha et al[20] may reflect the small number of participants treated with CEE alone (n = 8 in the CEE group) or perhaps differential ability of CEE to suppress testosterone compared to estradiol. All included studies were retrospective, may have been underpowered to detect a difference between groups and not all accounted for estradiol dose and estradiol concentrations when performing statistical comparison between groups.

4.3 | Body fat redistribution

Body composition is readily measurable by anthropometry and whole-body DXA in the research setting. A large prospective observational study described the changes in body fat distribution that occur with the commencement of feminizing therapy (predominantly with estradiol and cyproterone acetate) with no comparator group.[21] In this cohort, there was an increase of 18% in the android region, 42% in the leg region and 34% in the gynoid region and a −0.03 decrease in waist-to-hip ratio due to an increase in hip circumference.[21] The study by Gava et al[18] included in this review showed no difference in body composition changes in those treated with estradiol plus either CPA or leuprolide. However, the study may have been underpowered to detect such a difference and did not describe body fat redistribution by body region (android or gynoid). While CPA has additional androgen receptor antagonism compared to GnRH analogues, it is possible that the androgen receptor modulation is less important at the low serum testosterone concentrations achieved in both treatment groups.

4.4 | Breast development

Breast development, a predominant desire of many transgender women, is not measured in a standardized, objective and reproducible manner making data comparison difficult between studies. Additionally, breast development may not be routinely recorded at follow-up clinical visits due to the sensitive and intimate nature of physical examination, limiting the utility of retrospective case review studies. Some transgender women may also have breast augmentation surgery, limiting the ability to discern the effects of oestrogens and antiandrogen therapy. Various methods have been used in available studies to assess breast development, including self-assessed and clinician assessed Tanner stage, calculation of cup size using

measurements of chest and breast circumference and qualitative assessment with photography.

No eligible studies assessed breast development in a manner that allowed robust comparison between different antiandrogens. However, De Blok et al[22] provided insight into timing of breast development in a retrospective study of 229 transgender women taking estradiol plus CPA 50-100 mg daily or spironolactone 100-150 mg daily. Breast development (measured breast circumference and calculated cup size) was evaluated over a 12-month period following initiation of estradiol and antiandrogen therapy. This study did not stratify breast development by antiandrogen, though it is likely that most participants received CPA given it forms standard care in the ENIGI treatment protocol.[6] Nonetheless, results showed that breast development predominantly occurred within the first 6 months of therapy, with an average increase in breast circumference of 1.8 cm (1.4-2.3) over the first 3 months, and 1.3 cm (0.9-1.8) over the following 3 months. At 12 months, 48.7% of participants had a cup size less than AAA (<8 cm) and only 7 participants (3.6%) had a cup larger than A (12-14 cm). Additionally, Prior et al[4] used self-reported cup size and clinical photography to document breast development with estradiol, MPA and spironolactone therapy over 12 months. An A cup size was reported in 'most subjects', though detailed data was not published. Difficulties in analysing photographic data in a quantitative way limited statistical comparison, though images provided a qualitative depiction of the potential effects of feminizing therapy.

Breast development in cis- and transgender women was recently reviewed by Reisman et al[23] The significant ductal and lobuloalveolar growth and fat deposition that occurs during puberty is regulated by local growth factors and hormones. Estradiol is principally responsible, with lesser contributions from growth hormone and glucocorticoids needed for normal breast development.[24,25] Progesterone and prolactin play additional roles in the alveolar branching and proliferation of breast tissue that occurs during pregnancy in preparation for lactation.[25] Gynaecomastia occurs commonly in cisgender boys during puberty and may occur in cisgender men due to endocrinopathies or androgen deprivation therapy and is attributed to a relative increase in the oestrogen to androgen ratio.[25] Interestingly, the histological changes observed in cis-gender men with gynaecomastia differ from transgender women treated with ethinylestradiol plus either CPA or orchiectomy in a small case series.[26] The authors suggest that the use of exogenous estradiol and progestogens may be required to achieve complete acinar and lobular formation, though there is limited high-quality data to support this assertion.[26] Given the perceived importance of increasing the oestrogen to androgen ratio, it is plausible that an antiandrogen causing more potent antagonism of the androgen receptor, or more significantly lower testosterone levels may contribute to enhanced breast development in transgender women.

4.5 | Facial and body hair reduction

Similarly, changes in facial and body hair are not measured in a consistent manner to allow comparison across studies, and those that use techniques with high fidelity are highly labour intensive. Self-reported changes in facial and body hair, or clinical tools such as the modified Ferriman-Gallwey score are used in some studies but are limited by the subjective nature of responses and removal of unwanted facial and body hair by transgender women. No eligible studies assessed changes in facial and body hair adequately to allow comparison of antiandrogens in transgender women.

Notably, Giltay & Gooren[27] performed a prospective study of 21 transgender women treated with estradiol plus CPA 100 mg daily for 12 months, examining changes in facial and body hair. Body hair growth and distribution were assessed using a modified Ferriman-Gallwey score of androgen-dependent areas. Clinical photography images taken with a macro lens of the face and periumbilical region were analysed to calculate hair growth per day, hair diameter and hair density. The modified Ferriman-Gallwey score significantly decreased from baseline (21/36) to 12 months (10/36) ($P < .001$). The hair growth rate, diameter and density were significantly lower in the periumbilical region ($P < .001$) and facial region ($P = .009$, $P = .049$ & $P = <.001$ for hair growth rate, diameter and density, respectively) over a 12-month period. The lack of a comparator group limited the ability to discern the effects of antiandrogen therapy from estradiol. Prior et al[4] attempted to document changes in facial hair with estradiol, MPA and spironolactone therapy in 50 transgender women with clinical photography. However, difficulties analysing images in a quantitative manner limited interpretation of results, as did confounding effects of high dose estradiol therapy in many participants prior to enrolment and co-administration of MPA.

The interaction between androgens (particularly testosterone and dihydrotestosterone) and the androgen receptor present in some pilosebaceous units promotes differentiation into pigmented terminal hair follicles.[28] This results in the typical male pattern of facial and body hair. Paradoxically, androgenetic alopecia or male pattern baldness is also androgen-dependent, attributed to the miniaturization of terminal hair follicles and suppression of scalp hair growth in genetically predisposed individuals.[28,29] By reducing levels of the more potent androgen dihydrotestosterone and therefore reducing interaction with the androgen receptor in hair follicles, 5-alpha reductase inhibitors are effective in the treatment of androgenic alopecia in cisgender men.[30] While 5-alpha reductase inhibitors are recommended by some clinicians for transgender women with pre-existing male pattern baldness,[31] there is no high-quality evidence in this population to suggest superiority of 5-alpha reductase inhibitors in achieving regrowth of scalp hair or reductions in facial and body hair compared to other antiandrogens. Given standard feminizing therapy is able to achieve substantial reductions in androgen activity and/or androgen levels, there may be limited added benefit in further reducing production of dihydrotestosterone with 5-alpha reductase inhibition. In contrast, 5-alpha reductase inhibitors may be effective in treating androgenetic alopecia in transgender men treated with testosterone, though it is unclear whether this may decrease other masculinizing effects of testosterone therapy such as the growth of facial and body hair.[32]

4.6 | Extrapolation of antiandrogen use in other patient populations

Insights may be gained from the extrapolation of evidence related to the use of antiandrogens in women with hirsutism/polycystic ovarian syndrome (PCOS) and men with prostate cancer. Like transgender women, antiandrogens may be used together with oestrogen for the treatment of excess facial and body hair in cisgender women. Guidelines for the treatment of PCOS recommend the use of an antiandrogen as second-line treatment in combination with the oral contraceptive pill (OCP) if there has been an inadequate cosmetic response after 6 months of treatment, or as monotherapy in the presence of significant contraindications or intolerance to the OCP.[33,34] Small randomized controlled trials have shown that spironolactone, flutamide and finasteride are more effective than placebo at reducing the modified Ferriman-Gallwey score and hair shaft diameter in women with moderate to severe hirsutism.[34,35] CPA use has also been associated with significant reductions in hirsutism, when used at low doses (ethinylestradiol/CPA 2 mg daily) and high doses in combination with the OCP.[36] Recently, the addition of bicalutamide 50 mg daily to the OCP did not significantly decrease the modified Ferriman-Gallwey score compared to placebo in women with PCOS but did significantly decrease the hair density assessed by videodermoscopy.[37] Currently, available evidence does not support the use of one antiandrogen over another for the treatment of hirsutism.[34,36] Additionally, women with hirsutism/PCOS are typically treated with synthetic oestrogens (principally ethinylestradiol) and progestins as part of the OCP and have lower baseline serum total testosterone concentrations than transgender women, limiting the generalizability of findings.

Androgen deprivation therapy is commonly used for the treatment of prostate cancer. Use of GnRH agonists/antagonists to decrease testosterone synthesis form standard care for advanced prostate cancer and may be combined with nonsteroidal androgen receptor antagonists to inhibit interaction with the androgen receptor.[38] A review of men treated for prostate cancer showed much higher rates of gynaecomastia in men treated with nonsteroidal androgen receptor antagonists (flutamide 30%-79%, nilutamide 79%) compared to treatment with GnRH analogues (goserelin 1%-5%, leuprolide 13%-16%), combined androgen blockade (flutamide plus GnRH agonist 13%-22.8%) or CPA (6%-7.2%). These findings are consistent with current understandings of the pathophysiology of gynaecomastia, attributed to a relative increase in oestrogenic activity and decrease in androgenic activity which is amplified by the aromatization of increased testosterone to estradiol with use of nonsteroidal androgen receptor antagonists. A reduction in lean body mass and increase in fat mass was observed following initiation of androgen deprivation therapy with GnRH analogues, like changes described in transgender women. Given treatment recommendations for antiandrogens in prostate cancer are guided by improved progression-free survival rather than side effects of feminization, and that oestrogen therapy is used concurrently in transgender women, extrapolation of these findings is limited.

4.7 | Safety considerations

While detailed discussion of the relative safety of antiandrogens is beyond the scope of this review, this will of course also influence antiandrogen prescribing practices. Severe and fatal hepatotoxicity has been reported in patients treated with flutamide, CPA, and rarely bicalutamide in the prostate cancer literature.[39] However, reported cases of severe hepatoxicity with CPA have occurred at doses of at least 100 mg daily,[39] which is higher than the doses typically used for transgender women. Additionally, use of CPA in transgender women has been associated with a four times higher incidence rate of meningioma when compared to a female reference population, thought to be related to the expression of progesterone receptors in human meningiomas and the potent progestogenic activity of CPA.[40] This risk appears to be associated with cumulative dose exposures greater than 3 g.[41] While meningiomas are rare, both the European Medicines Agency[42] and the United Kingdom Medicines and Healthcare Products Regulatory Agency[43] have issued statements this year advising against use of CPA at doses of 10 mg daily or greater unless there are no other treatment options. CPA use has been associated with hyperprolactinaemia of uncertain clinical significance, which is typically reversible following discontinuation.[44] A fourfold increase in the incidence of prolactinomas was also been observed in transgender women compared to female reference populations, most of whom were taking CPA. However, it is unclear whether this represents a true increase in incidence or if it is reflective of increased prolactin monitoring in this population as the incidence of symptomatic prolactinomas was similar.[40]

4.8 | Strengths and limitations

The main outcome of this review is to highlight the lack of high-quality studies in the transgender health literature, particularly in relation to the optimal use of antiandrogens in transgender women. Indeed, there were no randomized controlled trials, perhaps reflecting the relative infancy of the transgender health literature. Existing studies are mostly retrospective analyses of clinic data, with a small number of study participants, lacking clinically relevant endpoints and without adequate comparison to different treatment groups. Instead, the serum total testosterone concentration is typically reported as a surrogate marker of therapy, a significant flaw given some commonly prescribed antiandrogens work predominantly via androgen receptor antagonism rather than decreasing testosterone levels. The results of this review emphasize the need for prospective randomized controlled studies to optimize the effective and safe delivery of gender-affirming care using clinically meaningful endpoints.

5 | CONCLUSION

Antiandrogens are frequently added to estradiol to assist with feminization and suppression of testosterone. Spironolactone,

CPA, GnRH analogues and MPA all have antiandrogenic effects and despite less suppression of total testosterone with spironolactone, there are inadequate data to support enhanced feminization with any particular antiandrogen. Serum total testosterone is a flawed surrogate marker of antiandrogen therapy given some medications work predominantly through androgen receptor antagonism rather than by decreasing testosterone levels. The comparative effects on breast development, body fat redistribution and reduction in facial and body hair are unclear. Further research is needed with clinically relevant endpoints to optimize the care of transgender women.

CONFLICT OF INTEREST

The authors have nothing to disclose.

AUTHOR CONTRIBUTION

LMA conceptualized scope of systematic review, developed the search strategy, performed the search literature search, screening and full-text review of records, discussed studies for inclusion and drafted the manuscript. BJN performed an independent literature search, screening and full-text review of records, discussed studies for inclusion and assisted with editing of the manuscript. JDZ assisted with manuscript editing and preparation. ASC assisted with conceptualization of the systematic review, provided guidance on the search strategy, arbitrated in the event of disagreement between LMA and BJN on studies for inclusion and assisted with editing of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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