Final Report – Endocrine Society of Australia 2019 Postdoctoral Award

Awardee: Dr Ada Cheung

Administering institution: The University of Melbourne

Project title: A randomised controlled trial comparing the effectiveness of anti-androgens in transgender women

I was honoured to have received the Endocrine Society of Australia Postdoctoral Award for 2019 which has enabled me to initiate this clinical trial which is now mid-recruitment. The funding from the ESA Postdoctoral award has enabled us to finalise ethics and governance approvals, engage a research nurse to manage the study, establish blinded research trial medications for this randomised controlled trial. In addition, the seed funding from ESA enabled me to obtain a further successful research grant from the RACP which will enable me to complete the study. We have now recruited a total of 18 participants out of 64 and conducted 45 study visits. Recruitment is progressing well and we are on target to complete the study on time and in line with our budget.

I have published the following publications which have gratefully acknowledged the ESA Postdoctoral Award for funding support:

1. Angus LM, Nolan BJ, Zajac JD, Cheung AS. A systematic review of anti-androgens and feminisation in transgender women. *Clin Endocrinol (Oxf)* 2020 doi: 10.1111/cen.14329.
2. Nolan BJ, Leemaqz SY, Ooi O, Cundill P, Silberstein N, Locke P, Grossmann M, Zajac JD, Cheung AS. Prevalence of polycythaemia with different formulations of testosterone therapy in transmasculine individuals. *Intern Med J.* 2020 Apr 1. doi: 10.1111/imj.14839. [Epub ahead of print]
3. Cheung AS, Leemaqz SY, Wong JP, Chew D, Ooi O, Zwickl S, Cundill P, Silberstein N, Locke P, Grayson R, Zajac JD, Pang KC. Non-Binary and Binary Gender Identity in Australian Trans and Gender Diverse Individuals. *Arch Sex Behav.* 2020 Oct;49(7):2673-2681. doi: 10.1007/s10508-020-01689-9.
4. Bretherton I, Grossmann M, Leemaqz SY, Zajac JD, Cheung AS. Australian endocrinologists need more training in transgender health: A national survey. *Clin Endocrinol (Oxf).* 2020 Mar;92(3):247-257. doi: 10.1111/cen.14143.
5. Zwickl S, Wong A, Bretherton I, Rainier M, Chetcuti D, Zajac JD, Cheung AS. Health Needs of Trans and Gender Diverse Adults in Australia: A Qualitative Analysis of a National Community Survey. *Int J Environ Res Public Health* 2019 *16(24):5088* doi: 10.3390/ijerph16245088.
6. Angus L, Leemaqz S, Ooi O, Cundill P, Silberstein N, Locke P, Zajac JD, Cheung AS. Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving estradiol therapy. *Endocr Connect* 2019; 8(7):935-940. http://dx.doi.org/10.1530/EC-19-0272
7. Bretherton I, Thrower E, Grossmann M, Zajac JD, Cheung AS. Cross-sex hormone therapy in Australia: the prescription patterns of clinicians experienced in adult transgender healthcare. *Intern Med J* 2019 Feb;49(2):182-188. doi: 10.1111/imj.14035.
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9. Nolan BJ and Cheung AS. Relationship between serum estradiol concentrations and clinical outcomes in transgender individuals undergoing feminising hormone therapy: a narrative review. *Transgend Health* 2020 [accepted 3rd September 2020]

10. Thrower E, Bretherton I, Pang KC, Zajac JD, Cheung AS. Prevalence of autism spectrum disorder and attention-deficit hyperactivity disorder amongst individuals with gender dysphoria: a systematic review. *J Autism Dev Disord* 2020 Mar;50(3):695-706. doi: 10.1007/s10803-019-04298-1.
11. Chew D, Tollit MA, Poulakis Z, Zwickl S, Cheung AS, Pang KC. Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile. *Lancet Child Adolesc Health* 2020 Apr;4(4):322-330. doi: 10.1016/S2352-4642(19)30403-1. Epub 2020 Jan 21.
12. Cheung AS, Wynne K, Murray S, Erasmus J, Zajac JD. Position statement on the hormonal management of transgender and gender diverse individuals in Australia. *Med J Aust* 2019 Aug;211(3):127-133. doi: 10.5694/mja2.50259.
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5 UNSOLICITED REVIEW

WILEY

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.

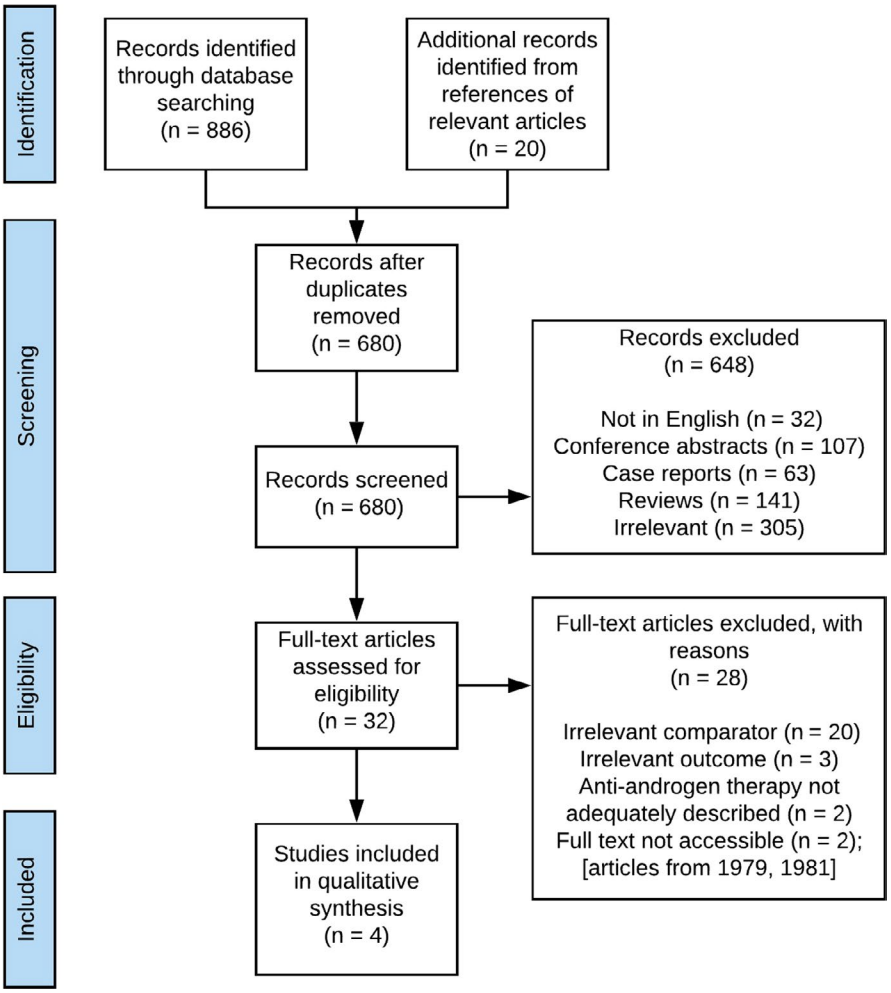

FIGURE 1 Flow diagram detailing systematic review process including identification and screening of records, assessment for eligibility and inclusion in review

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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Prevalence of polycythaemia with different formulations of testosterone therapy in transmasculine individuals

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Abbreviations: AUC, area under the curve; ENIGI, European Network for the Investigation of Gender Incongruence; GAHT, gender-affirming hormone therapy; LC-MS, Liquid chromatography-mass spectrometry; NATA, National Association of Testing Authorities

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ABSTRACT

Background: Masculinising hormone therapy with testosterone is used to align an individual's physical characteristics with their gender identity. Testosterone therapy is typically administered via intramuscular or transdermal routes and polycythaemia is the most common adverse event.

Aims: To compare the risk of polycythaemia with different formulations of testosterone therapy in transmasculine individuals.

Methods: A retrospective cross-sectional analysis was undertaken of transmasculine individuals at a primary and secondary care clinic in Melbourne, Australia. 180 individuals who were on testosterone therapy for >6 months were included. Groups included those receiving (1) intramuscular testosterone undecanoate (n=125), (2) intramuscular testosterone enantate (n=31), or (3) transdermal testosterone (n=24). Outcome was prevalence of polycythaemia (defined as haematocrit >0.5).

Results: Mean age was 28.4 (8.8) years with a median duration of testosterone therapy 37.7 (24.2) months. 27% were smokers. There was no difference between groups in serum total testosterone concentration measured. Whilst there was no difference between groups in haematocrit, there was a higher proportion of patients with polycythemia in those who were on intramuscular testosterone enantate (23.3%) than on transdermal testosterone (0%), p=0.040. There was no statistically significant difference in polycythaemia between intramuscular testosterone undecanoate (15%) and transdermal, p=0.066 nor between intramuscular testosterone enantate and undecanoate, p=0.275.

Conclusions: One in four individuals treated with intramuscular testosterone enantate and one in six treated with testosterone undecanoate had polycythaemia. No individual treated with transdermal testosterone had polycythaemia. This highlights the importance of regular monitoring of haematocrit in transmasculine individuals treated with testosterone and findings may inform treatment choices.

INTRODUCTION

Testosterone therapy is a necessary component of management for some transmasculine individuals to align their physical characteristics with their gender identity. Standard formulations and doses of testosterone used to treat hypogonadal men are recommended for gender transition (1, 2). Polycythaemia, a risk factor for venous and arterial thrombosis, is the most frequent adverse event of testosterone therapy in hypogonadal men (3), and is also commonly reported in observational studies of transmasculine individuals (4, 5).

A systematic review of 8 predominantly cohort studies found that testosterone therapy was associated with modest increases in haematocrit, although the quality of evidence was limited by small sample sizes, and little data on differential effects of testosterone formulations (4). The only randomized open-label trial compared transdermal testosterone with 2 formulations

of intramuscular testosterone in 45 individuals but was not powered to detect a difference in haematocrit (6). One prospective study measuring changes in haematocrit following initiation of gender-affirming hormone therapy (GAHT) found short-acting testosterone esters were associated with the highest prevalence of polycythaemia compared to both long-acting intramuscular testosterone and transdermal testosterone (7).

This is of concern given that in the general population, large epidemiological studies have demonstrated associations between elevated haematocrit and venous and arterial thrombosis in both sexes, even after adjustment for factors such as age, physical activity, and cardiovascular risk factors (8). The risk of cardiovascular disease is more than two-fold greater in high- versus low-haematocrit groups (9) and haematocrit levels in cisgender men of 0.46 or higher (0.42 or higher in cisgender women) are associated with greater than two-fold increased risk of unprovoked venous thromboembolism (10). Moreover, haematocrit predicts mortality in hypertensive men and women (10, 11). These findings have particular implications for transmasculine individuals given reports of an increased prevalence of cardiac events compared to cisgender women (12, 13) and men (13), after adjustment for other recognised risk factors.

As such, in this retrospective study of transmasculine individuals newly presenting to gender clinics who had been treated with testosterone for at least 6 months, we aimed to compare the prevalence of polycythaemia with different testosterone formulations (intramuscular testosterone undecanoate, intramuscular testosterone enantate, and transdermal testosterone gel).

METHODS

A retrospective audit of electronic medical records was performed of consultations for gender dysphoria at a primary care clinic and an endocrine specialist clinic in Melbourne, Victoria, Australia. Data were collected from consecutive new consultations between 1st January 2011 and 31st December 2016. The study was approved by the Austin Health Human Research Ethics Committee (LNR/17/Austin/102) and Thorne Harbour Health Community Research Endorsement Panel (THH/CREP 19/015) and the nature of the study did not require informed consent.

Clinical characteristics of the audit have been previously published (1). This cross-sectional analysis included transmasculine individuals newly presenting to the clinics who had been treated with masculinising hormone therapy with testosterone for at least 6 months and had fasting serum sex steroid results available within 1 month of their initial consultation. Testosterone formulations included 1000 mg intramuscular testosterone undecanoate, 250 mg intramuscular testosterone enantate, and transdermal testosterone gel.

The primary outcome of interest was prevalence of polycythaemia. While it is unknown what haematocrit should be targeted in transmasculine individuals, or the haematocrit at which the risk of cardiovascular events increases (3), we defined polycythaemia as haematocrit > 0.5 at any time point during GAHT, as described in the US Endocrine Society clinical treatment guidelines for the treatment of gender incongruent individuals (1).

Serum total testosterone concentration and haemoglobin was also recorded. As data were obtained retrospectively, sex steroid concentrations and haemoglobin were measured using several different immunoassays available as standard care for clinical decision-making. Only

laboratories accredited by National Association of Testing Authorities (NATA, the national accreditation body for Australia) were used.

Statistical analyses were performed using R (v3.5.1; R foundation for statistical computing). Mean (SD) or median (IQR) are reported as appropriate. Differences in haematocrit between testosterone formulations were tested using Kruskal-Wallis test followed by Nemenyi post-hoc comparisons and Fisher's exact test was performed for polycythaemia with Bonferroni adjusted pairwise comparisons. $p < 0.05$ was considered statistically significant.

RESULTS

Data were collected from 249 individuals, of whom 180 had adequate data available for analysis. Baseline characteristics are demonstrated in Table 1. Testosterone undecanoate (1000mg at 8-14-weekly intervals) was the most frequently prescribed formulation of testosterone (Table 2) followed by testosterone enantate (250mg at 2-3-weekly intervals). There was no significant difference between groups in median serum total testosterone concentration measured (11.5 nmol/L (1.7-21.1) for testosterone undecanoate, 12.1 nmol/L (1.35-20.45) for testosterone enantate and 5.6 nmol/L (1.1-17.1) for transdermal testosterone, overall p=0.347. Box plots of total testosterone concentration by testosterone formulation are shown in Figure 1.

Testosterone concentration, haemoglobin and haematocrit for each testosterone formulation are shown in Table 2. There was no difference in mean haematocrit or haemoglobin between the testosterone formulations (Table 2). Box plots of haematocrit by testosterone formulation are shown in Figure 2. There was a higher proportion of patients with polycythemia in those who were on intramuscular testosterone enantate (23.3%) than on transdermal testosterone

(0%), p=0.040. There was no statistically significant difference in polycythaemia between intramuscular testosterone undecanoate (15%) and transdermal (0%), p=0.066 nor between intramuscular testosterone enantate and undecanoate, p=0.275. There was an overall difference in haematocrit between groups, p=0.033. Of the individuals with polycythaemia, 3/30 (10%) individuals treated with testosterone enantate and 2/122 (1.6%) individuals treated with testosterone undecanoate had haematocrit >0.54. The maximum measured haematocrit was 0.58 in an individual treated with testosterone enantate.

DISCUSSION

In this retrospective cross-sectional analysis of testosterone treatment for transmasculine individuals attending gender clinics in Australia, there was a higher prevalence of polycythaemia in individuals using intramuscular testosterone enantate compared with transdermal testosterone. This difference was evident despite no measured differences in median total testosterone concentrations between the three formulations of testosterone therapy.

Physiological considerations

Although there is a breadth of data regarding the risk of polycythaemia with exogenous testosterone in hypogonadal men, it is important to establish the risk in transmasculine individuals. Physiological differences include a lower baseline haemoglobin and haematocrit in transmasculine individuals (14), and differential effects of exogenous testosterone on endogenous testosterone production (15). In individuals assigned male at birth, exogenous testosterone supresses endogenous testosterone production, whereas circulating testosterone in those assigned female at birth is under less dynamic regulation and remains essentially unchanged following exogenous testosterone administration (15). Therefore, the measured

testosterone concentration in transmasculine individuals is a combination of both endogenous and exogenous testosterone.

Comparison with previous literature

Consistent with results from our study, previous reports in both transmasculine individuals and hypogonadal men have also found short-acting intramuscular testosterone formulations to be associated with the highest risk of polycythaemia (5, 16-18). A retrospective cross-sectional study of 50 transgender men on established GAHT (average duration 10 years), observed 14 individuals (28%) with an elevated haematocrit (5). The majority of men were treated with short-acting intramuscular testosterone esters (Sustanon), and these were found to be associated with higher haematocrit compared to intramuscular testosterone undecanoate or transdermal testosterone. The only prospective study examining changes in haematocrit following initiation of testosterone in transmasculine individuals enrolled 192 individuals through the European Network for the Investigation of Gender Incongruence (ENIGI) (16). Transgender men receiving short-acting testosterone esters (Sustanon) or testosterone gel had a larger increase in serum haematocrit and higher rate of polycythaemia (defined as haematocrit > 0.5) compared to men receiving testosterone undecanoate at 12 months follow-up (16). In total, 22 of 192 (11%) individuals developed a serum haematocrit greater than 0.50. No thromboembolic events were documented in either study.

Potential mechanisms for our findings

Mechanisms for the differences in prevalence of polycythaemia are likely multifactorial. Whilst our findings are based only on a single measurement, the observed difference in haematocrit may potentially be explained by factors such as the pharmacokinetic profiles or doses of the testosterone formulations. Short-acting intramuscular testosterone produces

significant supra-physiological concentrations in the days following administration, with significant falls in concentrations prior to the next injection (19, 20) leading to an overall increased area under the curve (AUC), whereas long-acting testosterone undecanoate has a more stable pharmacokinetic profile (19, 21). Transdermal testosterone was not associated with polycythaemia in our analysis, however previous studies in hypogonadal men have reported polycythaemia with transdermal testosterone, although it should be noted that these studies are in an older cohort of participants who are at higher risk of polycythaemia (22).

Clinical implications

Given the lack of data in the field, this study highlights potential increased risk of adverse events with short-acting testosterone formulations. This may influence treatment decisions, particularly in individuals with risk factors for, or those with established polycythaemia. Similarly, a trial of testosterone undecanoate or transdermal testosterone could represent an alternative for transmasculine individuals with polycythaemia on short-acting intramuscular formulations. Several individuals extended the duration between intramuscular testosterone undecanoate or changed formulation due to development of polycythaemia. However, we did not have longitudinal haematocrit data following the change to regimen.

Further prospective longitudinal studies are required to delineate the risk of polycythaemia, and haematocrit range that should be targeted in transmasculine individuals. Until further data is available, from a harm minimisation perspective, monitoring haematocrit in transmasculine individuals treated with testosterone is warranted to minimise potential adverse venous and arterial thrombosis risks. Consistent with this, the 2017 Endocrine Society Clinical Practice Guidelines acknowledge a “very high” risk of polycythaemia in

transmasculine individuals and recommend measurement of haematocrit at baseline, every 3 months for the first year and then 1-2 times per year thereafter. (23).

Limitations

There are multiple limitations to this analysis. Given the retrospective cross-sectional study design, there are inherent limitations including missing data (haematocrit (73/249), total testosterone concentration (69/249), dose frequency), an inability to determine time to rise in haematocrit and a lack of clinical features of masculinisation. Individuals were not randomized to testosterone formulation which could confound results, and we did not have details regarding rationale for the testosterone formulation used. Similarly, we cannot account for potential confounders including treating clinician, their preferences for testosterone therapy or active smoking status. Testosterone concentrations reported represent a single time point as part of routine clinical care so are not strictly collected in a standardized manner and we do not have data on compliance with therapy. Although testosterone was measured via immunoassay on different assays, all were performed using NATA-accredited laboratories. Liquid chromatography-mass spectrometry (LC-MS) is considered the reference standard for sex steroid measurement (24) but is not routinely available in clinical care. There were also small patient numbers treated with testosterone enantate and transdermal testosterone. However, this is representative of hormone prescription patterns in Australia (25). The clinical implications of polycythaemia were unable to be determined and further prospective studies are required.

CONCLUSIONS

One in four individuals treated with intramuscular testosterone enantate and one in six treated with testosterone undecanoate had polycythaemia. Polycythaemia was not present in those on

transdermal testosterone. Whilst regular monitoring of haematocrit in transmasculine individuals treated with standard doses of testosterone is recommended in guidelines, this may be more pertinent in those using intramuscular formulations. Further prospective longitudinal studies are required however these preliminary findings may influence treatment choices in individuals with risk factors for, or those with established polycythaemia.

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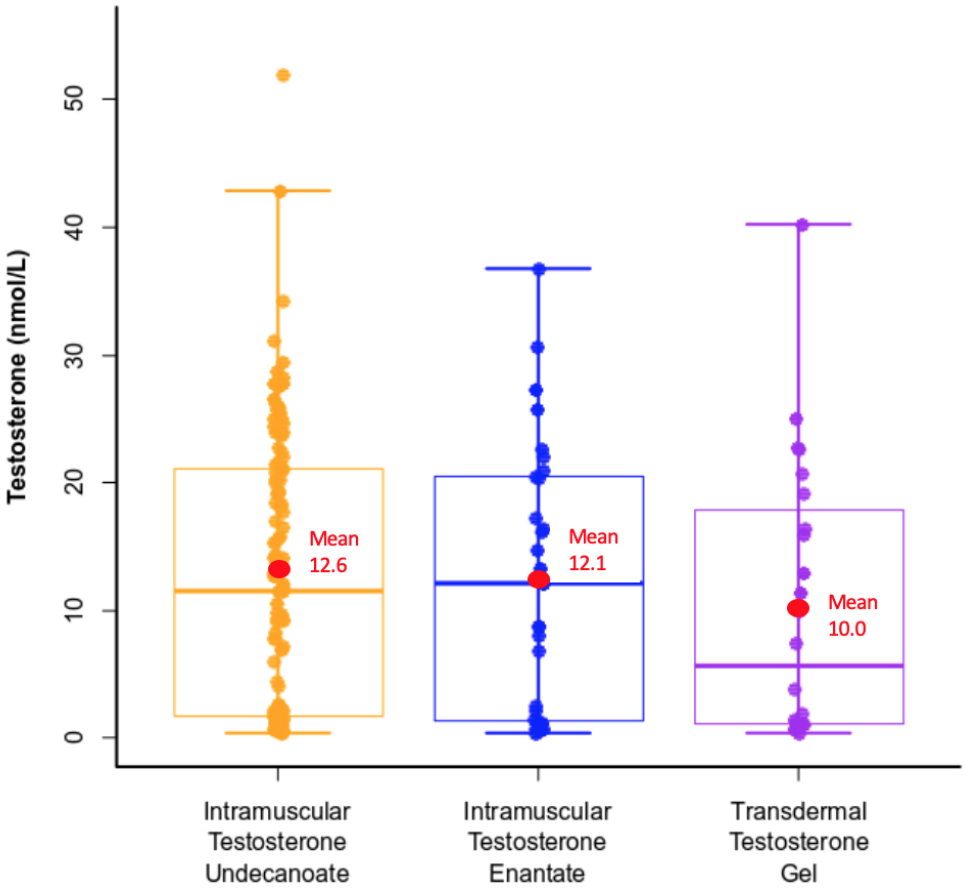

Figure 1: Total testosterone by testosterone formulation

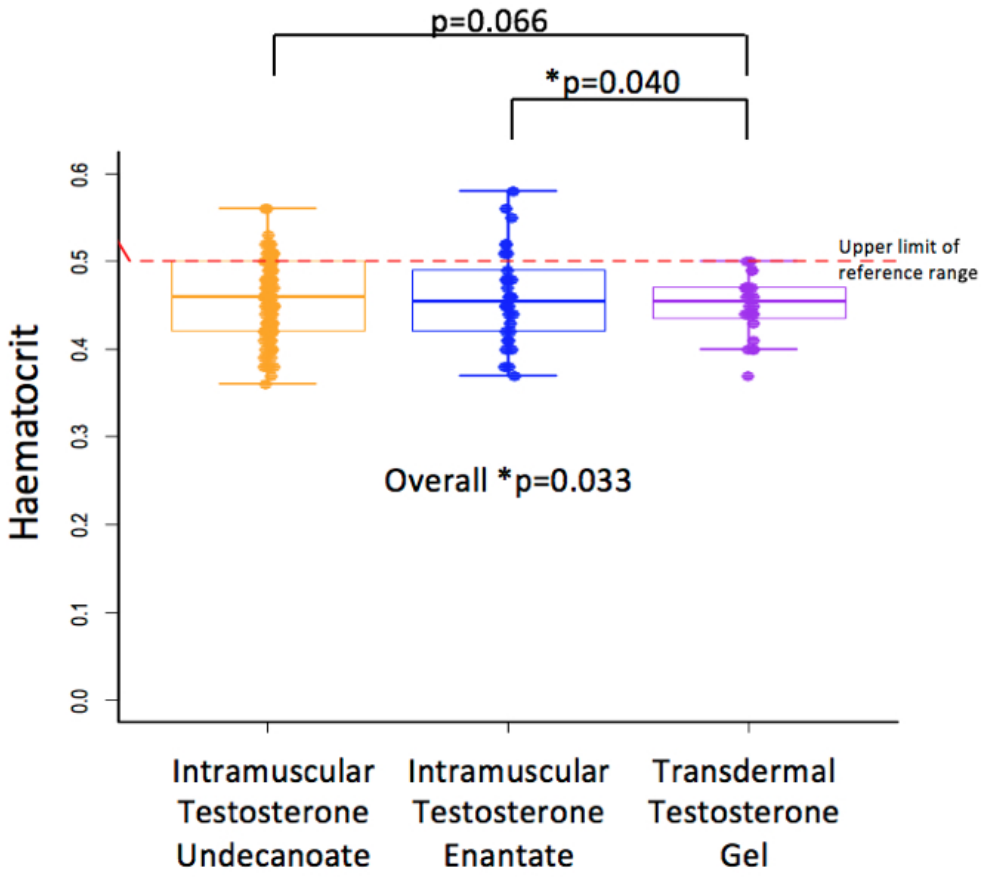

Figure 2: Haematocrit by testosterone formulation

238x208mm (72 x 72 DPI)

	Overall	Testosterone undecanoate	Testosterone enantate	Transdermal testosterone	P-value[#]
Age (years): mean (SD)	28.4 (8.8)	27.5 (8.3)	29.2 (10.2)	30.48 (11.5)	0.64
Duration of GAHT at initial review (months): median (IQR)	0 (0 – 11.0)	0 (0 – 11.0)	5 (0 – 33.8)	1.5 (0 - 32)	0.07
Smoking history (n=169)	46 (27%)	38/116 (33%)	4/30 (13%)	4/23 (17%)	0.06
Hypertension (n=157)	12 (7%)	6/110 (5%)	4/27 (15%)	2/20 (10%)	0.17
Hypercholesterolaemia (n=154)	21 (13%)	14/105 (13%)	5/29 (11%)	2/20 (14%)	0.77

Mean (SD) or median (IQR) are shown. Number (prevalence %) is shown for categorical variables. GAHT = gender-affirming hormone therapy. n = number of individuals for which data was available. [#] P-value from Kruskal-Wallis test for age and duration of GAHT, and Fisher's exact test for categorical variables.

Table 1: Clinical characteristics

385x341mm (72 x 72 DPI)

	Intramuscular testosterone undecanoate	**Intramuscular testosterone enantate**	**Transdermal testosterone**	**P-value**
Number (%)	125 (69%)	31 (17%)	24 (13%)	
Total testosterone (nmol/L): median (IQR) and mean (SD)	11.5 (1.7-21.1) 12.6 (10.8)	12.1 (1.35-20.45) 12.1 (10.4)	5.6 (1.1-17.1) 10 (10.8)	0.347
Haemoglobin (g/L)	146 (15)	148 (15)	144 (14)	0.848
Haematocrit	0.46 (0.04)	0.46 (0.05)	0.45 (0.03)	0.725

Mean (SD) or median (IQR) are presented. P values refer to overall difference between the groups obtained from the Kruskal-Wallis test.

Table 2: Hormone and haematology parameters with different testosterone formulations

383x238mm (72 x 72 DPI)

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ORIGINAL PAPER

Non-Binary and Binary Gender Identity in Australian Trans and Gender Diverse Individuals

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Abstract
Many trans and gender diverse (TGD) people have gender identities that are not exclusively male or female but instead fall in-between or outside of the gender binary (non-binary). It remains unclear if and how those with non-binary gender identity differ from TGD individuals with binary identities. We aimed to understand the sociodemographic and mental health characteristics of people with non-binary identities compared with binary TGD identities. We performed a retrospective audit of new consultations for gender dysphoria between 2011 and 2016 in three clinical settings in Melbourne, Australia; (1) Equinox Clinic, an adult primary care clinic, (2) an adult endocrine specialist clinic, and (3) the Royal Children's Hospital, a child and adolescent specialist referral clinic. Age (grouped by decade), gender identity, sociodemographic, and mental health conditions were recorded. Of 895 TGD individuals, 128 (14.3%) had a non-binary gender. Proportions differed by clinical setting; 30.4% of people attending the adult primary care clinic, 7.4% attending the adult endocrine specialist clinic, and 8.0% attending the pediatric clinic identified as non-binary. A total of 29% of people in the 21–30-year-old age-group had a non-binary gender identity, higher than all other age-groups. Compared to TGD people with a binary gender identity, non-binary people had lower rates of gender-affirming interventions, and a higher prevalence of depression, anxiety, and illicit drug use. Tailoring clinical services to be inclusive of non-binary people and strategies to support mental health are required. Further research to better understand health needs and guide evidence-based gender-affirming interventions for non-binary people are needed.

Keywords Transgender · Transsexualism · Gender identity · Gender dysphoria · Non-Binary

Introduction

Gender variance, or gender nonconformity is an umbrella term used to describe gender identity, expression, or behavior that falls outside of culturally defined masculine or feminine norms. In population-based studies, gender variance is estimated to occur in up to 4.6% of the general population (Ahs et al., 2018; Kuyper & Wijsen, 2014; Meerwijk & Sevelius, 2017; Van Caenegem et al., 2015; Zucker, 2017). As Western society's traditional concepts of gender have been challenged and evolved, the idea that there are many gender identities has been increasingly recognized. Consistent with this, it is now apparent that many trans and gender diverse (TGD) individuals have a gender identity that is not binary (male or female), but instead falls in-between, outside or beyond the gender binary (Richards et al., 2016; Thorne, Yip, Bouman, Marshall, & Arcelus, 2019). While the term non-binary can be used as a gender identity marker in itself, it is often used as an umbrella term—similar to genderqueer—that encompasses many gender identities that are temporarily or permanently neither exclusively masculine nor feminine (Koehler, Eyssel, & Nieder, 2018). This includes but is not limited to identities such as "agender" where someone does not identify themselves as having a particular gender, "gender fluid" where

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one's gender fluctuates, and non-binary "transmasculine" (or "transfeminine") where one does not identify as entirely male (or female), but identifies closer to the male (or female) end of the gender spectrum. We use the term non-binary in this article as an umbrella term to cover all gender identities that are not exclusively male or female.

The rapid rise in TGD individuals seeking health care over the past decade has been extensively documented and publicized worldwide (Ahs et al., 2018; Arcelus et al., 2015; Cheung et al., 2018; Delahunt, Denison, Sim, Bullock, & Krebs, 2018; Ewald et al., 2019). A less well known and more recent trend is an increase in the proportion of individuals presenting with a non-binary gender identity (Aparicio-Garcia, Diaz-Ramiro, Rubio-Valdehita, Lopez-Nunez, & Garcia-Nieto, 2018; Twist & de Graaf, 2019). There are a wide range of estimates of non-binary people which relate to generational differences and methodology. In the past, cohort studies of TGD individuals have demonstrated a predominance of transgender females (male-to-female) followed by transgender males (female-to-male) with few having non-binary identities (Gooren, Giltay & Bunck, 2008; van Kesteren, Asscheman, Megens, & Gooren, 1997). More recent surveys within the TGD community, specifically in people who identified with a gender that differed from their sex assigned at birth, revealed a much higher relative proportion of non-binary identities. A 2018 United Kingdom community survey of over 14,000 TGD people found almost 52% had a non-binary gender identity (Government Equalities Office, 2018) and the Canadian Trans Youth Health Survey involving 839 TGD participants found 41% identified as non-binary (Clark, Veale, Townsend, Frohard-Dourlent, & Saewyc, 2018). Up to 30% of TGD people attending our Australian primary care gender clinic now identify as non-binary (Cheung et al., 2018).

Despite this trend and the increasing visibility of people with non-binary identities in society, it remains unclear how people who have a non-binary gender identity differ from TGD people with a traditional binary identity. There is a lack of understanding of the unique health needs of people with non-binary identities or how to respectfully interact with them (Liszewski, Peebles, Yeung, & Arron, 2018). An online TGD community survey in Germany has suggested that those with a non-binary identity are younger in age than those with a binary identity (Koehler et al., 2018) which may be related to evolving terminology and societal acceptance in recent years. In addition to potential age or generational differences, non-binary people have been shown to receive less support from family and friends, and experience greater isolation and cyberbullying compared with other TGD people (Aparicio-Garcia et al., 2018) and may struggle to navigate a medical system which has been traditionally based upon binary transgender identities to access necessary gender-affirming interventions (Bradford et al., 2019). These factors may predispose to poor mental health among people with non-binary identities with potential to exacerbate already high rates of depression and anxiety in the TGD community (Cheung et al., 2018). Moreover, some people with non-binary identity may request partial masculinization or feminization to align their physical characteristics with their non-binary gender identity (Beek, Kreukels, Cohen-Kettenis, & Steensma, 2015). Certainly, people with non-binary identity have reported less hormonal and surgical treatments and were less likely to desire gender-affirming surgery than compared with TGD people with a binary gender identity (Koehler et al., 2018). The reasons for this are unclear but might relate to inability to access care or gender binarism, due to preconceived ideas from health care professionals of how TGD people should transition from one gender to another (Monro, 2019). Studies do not consistently demonstrate worse mental health outcomes among non-binary people. A study of 677 youth found that non-binary people were, in fact, less likely than binary TGD people to report suicidality, anxiety, and depression, and had higher levels of life satisfaction (Rimes, Goodship, Ussher, Baker, & West, 2019).

Given the inconclusive findings about non-binary people and an evolving social and health landscape, in order to guide the provision of gender-affirming care for individuals with a non-binary gender identity, we aimed to better understand the characteristics of people with non-binary compared with binary identities in relation not only to basic sociodemographic information, but also mental health problems and access to medical services. We hypothesized that individuals identifying as non-binary would: (1) be younger (given recent changes in societal understanding of gender), (2) have a higher prevalence of depression and anxiety, and (3) be less likely to receive medical intervention compared with individuals who identify with a binary transgender identity.

Method

Participants and Procedure

A retrospective audit of de-identified electronic medical records was performed of new consultations for gender dysphoria across three separate clinical settings in metropolitan Melbourne, Australia: (1) Equinox Gender Diverse Health Centre, an adult primary care general practice clinic which provides gender-affirming hormone therapy in addition to general medical care, (2) an adult endocrine specialist clinic (where patients are referred from primary care physicians for gender-affirming hormone therapy), and (3) the Royal Children's Hospital Gender Service (RCHGS), a statewide pediatric tertiary referral clinic for TGD children and adolescents under the age of 18 years. In Australia, primary care general practitioners are the first point of medical care for the

community and play a central role in delivery of health care. Given the need for a general practitioner's referral to attend a specialist service, the adult endocrine clinic is a secondary referral service which typically attracts more complex patients (i.e., individuals with comorbidities) for whom the primary care physician requests specialist input to manage their gender-affirming hormone therapy.

Measures

Only age at presentation and gender identity category (binary or non-binary) was available for the pediatric group. New consecutive consultations between 1 January 2011 and 31 December 2016 were analyzed. As the primary care clinic only commenced on 22 February 2016, data were analyzed for the first 12 months of operation until 22 February 2017. The study was approved by the Austin Health Human Research Ethics Committee (LNR/17/Austin/102) and the nature of the study did not necessitate informed consent.

Electronic medical records were reviewed collaboratively by two co-authors J. W. and D. C. and de-identified data were recorded. For the adult primary care and endocrine specialist clinics, sociodemographic and clinical data were extracted from electronic medical records obtained from consultation progress notes, and specialist correspondence as available. Gender identity and pronouns in use were self-reported on self-designed intake forms (question stated "Please indicate your gender identity/expression" with options to circle including female, male, trans, sistergirl, brotherboy, genderqueer, trans feminine, trans woman, trans masculine, trans man, non binary, prefer not to say, and/or "other (please specify)" with a free text section) used for all individuals at the primary care clinic, but gender identity was obtained from medical records for the pediatric and adult specialist clinics. As this was a retrospective file audit, the coding of gender identity for pediatric and adult specialist clinics was based on clinician notes, with patients self-reporting their gender identity. Age at presentation (grouped by decade), binary or non-binary gender identity, and birth-assigned sex were recorded. Those who had an unassigned gender identity were excluded. Binary gender identity was defined as identification as either male (including trans male, trans man, transgender male, and female-to-male) or female (including trans female, trans woman, transgender female, and male-to-female). All other identities were grouped as non-binary. While there are many gender identities, and non-binary is a gender identity in itself, for the purposes of this analysis, the term non-binary was used as an umbrella term to include all identities outside of the binary. Employment status, educational attainment, current smoking, hazardous alcohol intake (> 2 standard drinks per day), current illicit drug use, history of homelessness, mental health morbidities as well as previous suicidality were also recorded based upon diagnoses entered by treating clinicians into the medical records.

Statistical Analyses

Statistical analyses were performed using R (v3.5.1; R Foundation for Statistical Computing). The patient's sociodemographic and mental health characteristics were reported as frequencies and percentages for categorical variables, with associations between each characteristic and gender (non-binary vs binary) examined using χ^2 test or Fisher's exact test where appropriate. The analyses were corrected for multiple testing using the Bonferroni method. A logistic regression was performed to estimate the likelihood of identifying as a non-binary gender, compared to binary, across age groups. For all analyses, the significance level was set at 5%.

Results

A total of 902 new consultations were examined (adult primary care clinic $n = 257$, adult specialist endocrine $n = 283$, pediatric $n = 362$). The sociodemographic and clinical characteristics of the adult groups have been previously reported (Cheung et al., 2018). Seven individuals with an unassigned gender identity were excluded. A total of 895 individuals (age range 4–74 years) had data available for analysis of age distribution. A total of 533 individuals (age range 16–74 years) had clinical characteristics data available.

Non-Binary Gender Identities

Of 895 individuals, 128 (14.3%) reported a non-binary gender identity. Of these 128, 83 (64.8%) were birth-assigned female, 40 (31.3%) were birth-assigned male, and 5 (3.9%) preferred not to disclose their birth-assigned sex. Notably, the proportion of individuals with a non-binary identity varied depending on the clinical setting: with 30.4%, 7.4%, and 8.0% of patients identifying as non-binary at the adult primary care clinic, the adult endocrine specialist clinic, and the pediatric clinic, respectively. The range of non-binary gender identities and pronouns in use for the 99 adult individuals who attended the primary care and endocrine specialist clinics are listed in Table 1.

Age Distribution

People aged 21–30 years had the highest percentage of individuals with a non-binary gender identity (29.0%) compared with other age-groups (global test p value for age from logistic regression $p < .001$). The proportion of individuals with a non-binary gender identity was 8.1% in those < 21 years of

Table 1 Gender identities and preferred gender pronouns of study participants

Gender identity[a]	*n* (%)
Agender	3 (3.0%)
Androgynous	2 (2.0%)
Bigender	1 (1.0%)
Female	2 (2.0%)
Gender neutral	1 (1.0%)
Gender fluid	2 (2.0%)
Mx	8 (8.1%)
Non-binary/Genderqueer	68 (68.7%)
Trans	15 (15.2%)
Transfeminine	10 (10.1%)
Transmasculine	6 (6.1%)
Trans male/Trans man	3 (3.0%)
Other[b]	2 (2.0%)
Preferred not to say	2 (2.0%)
Unknown	6 (6.1%)
Pronoun used	
They	63 (63.6%)
She	9 (9.1%)
He	6 (6.1%)
They, She	6 (6.1%)
They, He	2 (2.0%)
They, She, He	2 (2.0%)
Name	2 (2.0%)
Other[c]	2 (2.0%)
Unknown	7 (7.1%)

[a]Individuals were allowed to indicate more than one gender identity, and thus, gender identities do not sum to 100%

[b]Other = Bakla ($n = 2$)

[c]Other = Ze/Hir ($n = 1$), En/En/Enself ($n = 1$)

age, 14.7% in people aged 31–40 years, and 3.0% in people aged 41 years and over.

Sociodemographic and Mental Health Characteristics

People with non-binary identities had a higher prevalence of a current diagnosis of depression and anxiety than TGD people with a binary gender identity but not other mental health conditions nor suicidality (Table 2). People with non-binary identity also had higher rates of current illicit drug use without any significant difference in smoking or hazardous alcohol use compared with binary identities. There was no significant difference in employment status, previous homelessness, or educational level attained. Of those who had non-binary identities ($n = 99$), there was no difference in any characteristic outlined in Table 2 when comparing those who were birth-assigned male compared to birth-assigned female.

Gender-Affirming Treatments

There were significantly fewer individuals with non-binary gender identity undergoing gender-affirming hormone therapy (53 of 99; 53.5%) than those with binary gender identity (399 of 434; 91.9%) ($\chi^2 = 89.28$; Bonferroni adjusted p value = .0001). Gender-affirming surgical procedures had been undertaken by 14 of 99 (14.1%) of people with non-binary identities, fewer than people with binary identities ($\chi^2 = 14.25$; Bonferroni adjusted p value for any surgical procedures = .0027). Mastectomy ($n = 11$) was the most common surgical procedure among people with non-binary identities followed by orchiectomy ($n = 1$), breast augmentation ($n = 1$), and laryngeal surgery for voice alteration ($n = 1$).

Discussion

This large cross-sectional study involving TGD adolescents and adults attending gender clinics in Australia found that overall 14.3% of individuals reported a non-binary gender identity, but the highest proportion were seen in those attending primary care clinics (30.4%). People in their third decade had the highest percentage of individuals with a non-binary gender identity compared to other age-groups. People with non-binary identity had a higher prevalence of having a current diagnosis of depression, anxiety, and illicit drug use as well as lower rates of hormonal and surgical interventions than TGD people with a binary gender identity.

Non-Binary Gender Identities

Rather than transitioning from one binary gender role to another, people with a non-binary gender identity identify outside of the gender binary, and may express a combination of masculinity and femininity or neither in their gender expression. There are few research reports on the prevalence of non-binary identities in the literature, likely in part related to the lack of capture of non-binary or genderqueer as a gender identity option in historical studies. If non-binary or "other" is not listed as an option for gender, then this subgroup of the TGD population will not be visible (Twist & de Graaf, 2019). The large 2008 U.S. National Transgender Discrimination Survey, a non-clinical sample involving 6450 trans and gender diverse people, found that 13% reported a non-binary identity (selecting the option "a gender not listed here") with the most common term specified as "genderqueer"(Harrison, Grant, & Herman, 2012). As compared to our clinical sample, this non-clinical survey is notably more inclusive of people that may have decided against treatment or engagement with our health services (Eyssel, Koehler, Dekker, Sehner, & Nieder, 2017). Of this group, 73% were birth-assigned female, which is similar to the predominance of birth-assigned females observed in our study and in others

Table 2 Sociodemographic and mental health characteristics of patients at adult primary care clinic and adult endocrine specialist clinic

Characteristic	Binary ($n=434$) n (%)	Non-binary ($n=99$) n (%)	χ^2	Bonferroni adjusted p value
Unemployment			0.23	ns
Employed/student	343 (79.0)	81 (81.8)		
Unemployed	91 (21.0)	18 (18.2)		
Experienced homelessness			2.02	ns
No	149 (34.3)	28 (28.3)		
Yes	41 (9.4)	14 (14.1)		
Tertiary education attainment			0.50	ns
No	111 (25.6)	25 (25.3)		
Yes	121 (27.9)	35 (35.4)		
Previous suicide attempt			4.03	ns
No	171 (39.4)	31 (31.3)		
Yes	41 (9.4)	16 (16.2)		
Depression			10.33	.0172
No	207 (47.7)	29 (29.3)		
Yes	227 (52.3)	70 (70.7)		
Anxiety			29.12	< .0001
No	284 (65.4)	35 (35.4)		
Yes	150 (34.6)	64 (64.6)		
Bipolar disorder			N/A	ns
No	419 (96.5)	96 (97.0)		
Yes	15 (3.5)	3 (3.0)		
Post traumatic stress disorder			1.20	ns
No	417 (96.1)	92 (92.9)		
Yes	17 (3.9)	7 (7.1)		
Borderline personality disorder			0.81	ns
No	408 (94.0)	90 (90.9)		
Yes	26 (6.0)	9 (9.1)		
Obsessive compulsive disorder			N/A	ns
No	425 (97.9)	96 (97.0)		
Yes	9 (2.1)	3 (3.0)		
Eating disorder			5.30	ns
No	425 (97.9)	92 (92.9)		
Yes	9 (2.1)	7 (7.1)		
Illicit drug use			9.22	.0340
No	157 (36.2)	41 (41.4)		
Yes	54 (12.4)	34 (34.3)		
Hazardous alcohol intake			0.002	ns
No	336 (77.4)	75 (75.8)		
Yes	41 (9.4)	10 (10.1)		
Current smoking			1.71	ns
No	296 (68.2)	62 (62.6)		
Yes	100 (23.0)	30 (30.3)		
Hormonal therapy			89.28	< .0001
No	35 (8.1)	46 (46.5)		
Yes	399 (91.9)	53 (53.5)		
Gender-affirming surgery			14.25	.0027
No	286 (65.9)	85 (85.9)		
Yes	148 (34.1)	14 (14.1)		

N/A = not applicable (Fisher's exact test performed due to low counts). The number [n (%)] varies between variables due to missing data. Diagnoses are based upon those listed by treating clinicians into th e medical records. Of those who had non-binary identities ($n=99$), there was no difference in any characteristic based on birth-assigned sex

including adolescent studies (Koehler et al., 2018; Twist & de Graaf, 2019). While both birth-assigned males and females have non-binary gender identities, reasons for a relative higher proportion of birth-assigned females reporting non-binary identity is unclear. Notably, clinical characteristics based on birth-assigned sex were no different among those with non-binary identities.

The disproportionately greater number of individuals with a non-binary gender identity (30.4%) in our community-based primary care clinic compared to the specialist clinics (7.4% in adult and 8.0% in pediatric) suggests that there may be higher numbers of people with non-binary identities in the general TGD community as opposed to those attending specialist secondary or tertiary care facilities. The findings may well be related to bias of greater numbers of people with non-binary identities accessing the primary care clinic. Alternatively, the overall 14.3% of TGD people with a non-binary identity may be an under recognition of the proportion of people with non-binary gender identity in the TGD community. Methodology of recording gender may also play a role in under detecting prevalence; rather than absolute specifications of gender identity terms as we used in this study, a visual analog scale of masculinity or femininity may allow greater expression of one's gender. If presented with visual analog scales of masculinity and femininity, even TGD people who identify with a binary gender typically do not identify as 100% masculine or feminine (Twist & de Graaf, 2019). From a clinical perspective, people with non-binary or genderqueer identities have reported narratives of misunderstanding and disrespect by health care providers, and often were pressured to assume a binary transgender identity in order to receive care (Lykens, LeBlanc, & Bockting, 2018). Future research inclusive of the breadth and fluidity of gender identity is needed to understand how best to capture and meet the care needs of people with non-binary gender identities.

Age Distribution

While a concept of gender is often formed in the early childhood years between the ages of 3 and 5 (Ruble et al., 2007), understanding the implications of one's gender is a process which may extend into adulthood and beyond. In an attempt to understand their social surrounds and relate to other members of their group, children begin to adhere to gender stereotypes and begin to incorporate their concept of gender into their own identity (Martin & Ruble, 2004). A relatively rigid concept of gender develops in early school years which may be related to being surrounded by a stereotypically binary view of gender in society (Martin & Ruble, 2004). As cognition, language, and maturity develop over time, a more critical exploration of gender and identity is likely to develop throughout adolescence and youth, particularly in recent years, as traditional gender stereotypes in society are increasingly being challenged. This may well account for our observation that the proportion of young people identifying with a non-binary gender peaks in young adulthood (ages > 20–30). Explanations for the relatively fewer people in older age groups who reported a non-binary identity require further study, but we postulate that more traditional views of gender as a binary may have prevailed in the past without common language or concepts to describe non-binary identity.

Furthermore, historical criteria for the diagnosis of gender identity disorder or gender dysphoria in order to access gender-affirming interventions have been binary focused, requiring individuals to have real life experience living as "the opposite sex" (Bockting, 2008). This is supported by reports that non-binary people have been pressured to provide a binary transgender identity to access care (Lykens et al., 2018).

Mental Health

TGD people as a whole already have extremely high rates of depression and anxiety, far higher than population prevalence rates, and higher than other mental health conditions such as eating disorders (Cheung et al., 2018; Australian Bureau of Statistics, 2018; Kennedy et al., 1994). Notably, it can be challenging to disentangle depression from anxiety with about 85% of patients with depression also experiencing symptoms of anxiety, while comorbid depression occurs in up to 90% of patients with anxiety disorders (Gorman, 1996–1997). Nonetheless, it remains alarming that the non-binary subgroup of TGD people have an even higher rate of depression and anxiety compared to those with binary identities. While we can postulate that stigma, lack of understanding and acceptance in the broader society of non-binary gender identities contribute to mental health morbidities as has been previously suggested (Aparicio-Garcia et al., 2018), the high rates of depression and anxiety detected are likely multifactorial. An inability to access health care likely contributes and prior studies have shown lower rates of health care utilization including lower rates of being up-to-date in annual wellness visits (Reisner & Hughto, 2019). Many gender services traditionally have binary treatment pathways, often requiring people to live as the opposite sex or undergo hormonal therapy prior to accessing gender-affirming surgery. These pathways are unlikely to suit people with non-binary identities and form a barrier to accessing necessary treatments to relieve a person's dysphoria, depression, and anxiety. Greater understanding of individual narratives from health care providers are required. We did not observe an elevated rate of attempted suicide compared to those with binary gender identities, but this may be a limitation of data collection methods used in this study. In non-clinical populations, suicidal ideation has been reported in a meta-synthesis to be lowest among those who are gender non-conforming

compared to trans female or trans male identities (Adams, Hitomi, & Moody, 2017).

The higher rates of illicit drug use observed in our study may represent an attempt to alleviate psychological distress and be a sign of unmet mental health needs (Smith et al., 2017). Higher rates of discrimination and major depression have been reported as being associated with illicit drug use (Carliner, Sarvet, Gordon, & Hasin, 2017; Choi, DiNitto, Marti, & Choi, 2016). Studies have suggested that in those with both depression and substance use, treatment of the depression often helps to alleviate the substance use disorder as well (Deas & Brown, 2006). Negative experiences among non-binary people in accessing health care (Lykens et al., 2018) may limit the engagement of non-binary people in mental health treatment programs which may potentially be improved with inclusive gender-affirming environments.

Gender-Affirming Treatments

Fewer non-binary people undergo medical or surgical intervention compared to binary TGD people (Koehler et al., 2018; Nieder, Eyssel, & Kohler, 2019). This can be attributed to a number of factors. Firstly, gender clinics have traditionally adhered to strict protocols for accessing hormonal and surgical gender-affirmation treatments which require individuals to have demonstrated a stable and consistent gender identity over time with a binary-focused treatment practice (Coleman et al., 2012). This, however, is inconsistent with the way some non-binary people (such as those who are genderfluid) experience their gender. Non-binary people vary greatly in their desires for medical and surgical intervention, including requests for partial masculinization or feminization to align their physical characteristics with their non-binary gender identity (Beek et al., 2015). Factors such as fear of discrimination or lack of health care provider understanding of non-binary identities may present barriers to non-binary people being able to access the health care they desire (Bradford et al., 2019; Monro, 2019; Zwickl et al., 2019). In addition, non-binary individuals may be less likely to access transgender health services due to inherent less gender incongruence and more body satisfaction (Jones, Bouman, Haycraft, & Arcelus, 2019). Non-binary people may not desire masculinization or feminization and may affirm their non-binary gender identity in other ways, including chest binding, clothing, and change of name and pronouns.

Importantly, some non-binary people will seek masculinizing or feminizing hormone therapy in a similar pathway to a binary trans man or trans woman, but for others, they may desire a lower dosage of hormone therapy or to use hormone therapy for a short, fixed period of time to achieve particular irreversible changes (such as voice lowering with testosterone therapy) (Vincent, 2019). Some non-binary people who often have higher levels of body satisfaction, may not desire hormonal therapy but require gender-affirming surgery (such as chest reconstructive surgery or mastectomy) to align their physical characteristics with their affirmed gender which may challenge traditional gender transition treatment pathways (Jones et al., 2019). While identity (binary versus non-binary) has a significant impact on the way people make sense of their bodies and what gender-affirming treatments they seek, further research should seek to unravel the reasons for differences observed such as whether there are differences between those that have accessed surgery compared to those that are yet to access.

Extensive discussions and considerations about individual desires and potential effects of interventions is required, in addition to the unknown long-term physical effects (such as low-dose treatments on bone health). Greater empathy for diversity in experienced gender and individual narratives will aid provision of a tailored, balanced approach to reduce barriers and binaries to gender-affirming care (Vincent, 2019). Further research incorporating gender non-binary patients are necessary to enable the development of treatment protocols and clinical guidelines to effectively guide the provision and monitoring of gender affirming interventions in this group of patients.

Limitations

There were several limitations to this study. The first is inherent to our retrospective cross-sectional design, since data were gathered from medical records, which meant that several parameters were based on self-reported clinical history or missing. The methodology may well have contributed to underreporting of individuals with non-binary gender identity and underreporting of attempted suicide, particularly in comparison with non-clinical samples. We did not have detailed information on the pediatric cohort, nor did we have information regarding social supports, or contributing factors to the increased rates of mental health morbidities observed. Electronic medical records were reviewed collaboratively by two co-authors; JW who reviewed the adult records and DC who reviewed the child and adolescent records, and coding was not reviewed independently. Finally, our results are only representative of a specific clinical sample of treatment-seeking gender non-binary individuals presenting to gender clinics and may not be generalizable to the wider community of non-binary individuals who do not access the types of clinical services assessed, or any services. Indeed, prospective studies are needed to further characterize the gender non-binary population and to confirm the differences in health and psychosocial disparities observed between gender non-binary individuals and TGD people with binary identities. Nonetheless, as there is a scarcity of research incorporating gender non-binary individuals, this large cohort of non-binary

people provides important descriptors which may guide clinical service delivery.

Conclusion

At present, non-binary identities are most frequently reported in young adults and those with non-binary identities are more likely to have mental health morbidities and use illicit substances. With increasing societal acceptance and challenging of conventional gender stereotypes, it is likely that there will be a substantial increase in the number of non-binary individuals presenting to clinical services seeking gender-affirming treatment in the future. Tailoring clinical services and research to be inclusive of non-binary people is required which will hopefully improve community confidence to be open about non-binary gender status and foster pride and positivity about individuality. Enabling visibility is critical and policymakers and health care providers need to ensure non-binary people are validated, affirmed and captured in data collection.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest

Ethical Approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Austin Health Human Research Ethics Committee (LNR/17/Austin/102) approved this study.

Informed Consent The nature of this retrospective study of medical records did not necessitate informed consent.

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ORIGINAL ARTICLE

WILEY

Australian endocrinologists need more training in transgender health: A national survey

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Abstract

Objective: An increasing number of trans and gender diverse (TGD) individuals are seeking gender-affirming hormone therapy for gender transition. Little is known about the levels of training, experience and confidence of endocrinologists in providing care and lack of training and experience is a potential barrier to individuals seeking appropriate and timely health care. We aimed to assess the level of training and confidence of Australian endocrinologists and trainees in the endocrine management of trans and gender diverse individuals in a representative sample.

Design: Endocrinologist and trainee members of the Endocrine Society of Australia were invited to participate in an anonymous 14-item survey. Of the 545 members, 147 clinicians (95 adult endocrinologists, 2 paediatric endocrinologists and 50 endocrinology trainees) responded.

Results: When presented with a scenario regarding commencement of gender-affirming hormone therapy, only 19% felt confident providing clinical care to TGD individuals. Compared to other areas of endocrinology, 75% felt less or not at all confident in commencing hormone therapy in a TGD patient. No training in transgender medicine during medical school or during their endocrinology training was reported by 96% and 60%, respectively. There were significantly higher levels of confidence in all aspects including performing a consultation in those who had previously seen a TGD patient. The desire for more training was high (91%).

Conclusions: These results highlight the shortfall in training in TGD health care amongst endocrinologists and show that prior clinical experience is associated with higher levels of confidence. Medical schools and endocrinology fellowship training programmes will need to adapt to meet the increasing demand for quality TGD health services.

KEYWORDS

Australia, education, endocrinologist, gender diverse, survey, trainees, training, transgender

1 | INTRODUCTION

Transgender (trans) including those who identify as gender diverse (TGD) is an umbrella terms for people whose gender identity or gender expression is different from what is typically associated with their sex assigned at birth.[1] There is increasing recognition that gender exists on a spectrum rather than a male/female binary. Gender-affirming hormone therapy (formerly referred to as cross-sex hormone therapy) is used to align a person's physical characteristics with their gender identity. The goal is to alleviate gender dysphoria, the distress many

TGD individuals experience when their gender identity is markedly and persistently incongruent from their birth-assigned sex.[2] An estimated 0.6%-1.2% of the population identifies as TGD,[3-5] and there is increasing demand for trans and gender diverse health care in Australia.[6,7]

Between 56% and 75% of transgender individuals have clinically diagnosed depression, and 48% have attempted suicide, rates far higher than the general population.[7-10] Timely access to hormone therapies is associated with better psychological functioning and less anxiety, depression and gender dysphoria.[11-13] Typically, feminization is achieved with oestradiol as well as suppression of endogenous sex hormones with gonadotropin-releasing hormone analogues or antiandrogen agents. Testosterone is used to promote masculinization. Endocrinologists have experience in prescribing hormone therapy and therefore often oversee this process. There are international transgender health guidelines to guide prescribing practitioners,[1,14] and the importance of gender-affirming hormone therapy is acknowledged by Endocrine societies worldwide.[11,12,15]

Despite this, significant barriers exist in TGD health care. A 2010 United States (US) study revealed 19% TGD individuals reported being refused medical care due to their transgender or gender nonconforming status[16] and a subsequent US survey involving 350 TGD people reported that 31% needed, but were not receiving, hormone therapy.[17] A 2015 survey of an Australian gender service found that the most commonly cited negative aspect of the clinic was the long waiting time to receive an appointment.[13]

Inability to find doctors who will provide gender-affirming care is a major concern for the TGD community.[17,18] This may stem from inadequate training as international studies show that adequacy of training of endocrinologists in managing TGD individuals is lacking.[18-20]

Assessing levels of training and confidence of doctors are important to guide change, and this has so far never been assessed in the Australian context. We therefore aimed to assess the amount of training and confidence of endocrinologists and advanced trainees in providing gender-affirming hormone therapy. We hypothesized that Australian endocrinologists receive insufficient training in TGD care and that there is a desire for further education. Given the increasing demand for transgender health services, we intend to use data collected to contribute to evidenced-based improvements in the design of training resources and ultimately improve health service provision for the TGD community.

2 | METHODS

This anonymous 14-item online survey of training needs in transgender health was developed by four clinical endocrinologists with expertise in this area. Authors drew from other relevant published studies when designing this survey.[19,21] The survey was open to Australian endocrinologists and endocrine advanced trainees between 1 June 2017 to 31 December 2017. The survey preamble and questions are included in full in Appendix 1.

All clinical members of the Endocrine Society of Australia, the main professional body for practicing endocrinologists (451 endocrinologists and 94 advanced trainees), were invited to complete the survey via a link to an online survey platform provider (SurveyMonkey). The survey was advertised via email in the Endocrine Society of Australia member bulletin and to attendees at an endocrine advanced trainee lecture series.

Univariate analysis using Cochran-Armitage test was used to compare the level of confidence in managing TGD individuals between Endocrinologists who had seen a TGD individual to those who

TABLE 1 Survey participant demographics

Characteristic	Number (%)
Male gender	50 (34.0%)
Female gender	97 (66.0%)
Other	0 (0%)
Australian State or Territory of residence	
Australian Capital Territory (ACT)	1 (0.7%)
New South Wales (NSW)	24 (16.3%)
Northern Territory (NT)	1 (0.7%)
Queensland	7 (4.8%)
South Australia (SA)	17 (11.6%)
Tasmania	2 (1.4%)
Victoria	72 (49.0%)
Western Australia (WA)	23 (15.7%)
Occupation	
Adult Endocrinologist	95 (64.6%)
Paediatric endocrinologist	2 (1.4%)
Endocrine Trainee	50 (34%)
Main place of practice	
Hospital-Tertiary	110 (74.8%)
Hospital Nontertiary	8 (5.4%)
Private clinic	26 (17.7%)
Other	3 (2.0%)
Number of TGD individuals ever seen	
None	21 (14.3%)
1-4	73 (49.6%)
5-9	24 (16.3%)
10-19	15 (10.2%)
>20	14 (9.5%)
Number of TGD individuals are currently under their care	
None	95 (64.6%)
1-4	35 (23.8%)
5-9	4 (2.7%)
10-19	5 (3.4%)
>20	8 (5.4%)

had not, and between endocrinologists who had read the Endocrine Society guidelines to those who had not.

The study was approved by the Austin Health Human Research Ethics Committee (HREC/17/Austin/372).

2.1 | Demographics

Demographic data of respondents were obtained, including gender, age range, state or territory of practice, type of endocrine specialist (adult, paediatric, trainee, other) and main place of practice (tertiary hospital, nontertiary hospital, private clinic, or other). Caseload (number of transgender patients currently treating) and experience (number of transgender individuals ever treated) was also obtained.

2.2 | Level of confidence

Participants were provided with a straightforward scenario to ascertain if they would be willing to prescribe hormone treatment for an individual with confirmed gender dysphoria (see Appendix 1). Clinicians were then asked to rate their level of confidence in undertaking a consultation with a TGD individual, including taking a history, as well as prescribing and monitoring gender-affirming hormone therapy (please note this was formerly known as cross-sex hormone therapy, which was the terminology used in the survey but has since been superseded based on community feedback and will be referred to as gender-affirming hormone therapy in this discussion) compared with other areas of endocrinology.

2.3 | Training and experience

Prior training (as a medical student, advanced trainee or as a qualified endocrinologist) in transgender health was quantified. Respondents were asked to self-rate the amount of training they had received (too much, adequate, not enough) and whether there was a desire for further training (yes, no, unsure). Knowledge of existing published international transgender care guidelines was assessed.

3 | RESULTS

Of 545 clinical Endocrine Society of Australia members, there were a total of 149 respondents (27.3%). Two were excluded as they were neither endocrinologists nor trainees (1 nurse practitioner, 1 general physician). The remaining 147 respondents included 95 adult endocrinologists, 2 paediatric endocrinologists and 50 endocrinology advanced trainees. Results are summarized in Tables 1, 2 and 3.

3.1 | Demographics

The responders were broadly representative of the gender ratio of Endocrine Society of Australia members (34% of responders identified as male and 66% as female. No participants selected the other/free text gender option.). The majority of participants (52%) were ages 30-39 years. The majority of responses came from the south-eastern states, and the majority worked in a tertiary hospital setting (75%). With regard to clinical experience, 14% had never seen a TGD individual in clinical practice, and only 65% had no TGD individuals currently under their care. Demographic data of the respondents are shown in Table 1.

3.2 | Level of confidence

When presented with a straightforward scenario of a patient formally diagnosed with gender dysphoria by a psychiatrist and referred by their GP for commencement of hormone therapy, 54% did

TABLE 2 Confidence and experience

Characteristic	Number (%)
Management preferences in response to scenario	
Prefer not to treat	1 (0.7%)
Refer to a colleague	80 (54.4%)
Consider treating	29 (19.7%)
Feel comfortable treating	28 (19.1%)
Unsure	8 (5.4%)
NA	1 (0.7%)
Confidence in trans medicine compared with other areas in Endocrinology Performing a consultation	
Not at all confident	37 (25.2%)
Less confident	62 (42.2%)
Reasonably confident	42 (28.6%)
More confident	6 (4.1%)
Taking a history	
Not at all confident	20 (13.6%)
Less confident	57 (38.8%)
Reasonably confident	61 (41.5%)
More confident	8 (5.4%)
Commencing cross-sex hormone therapy	
Not at all confident	69 (46.9%)
Less confident	41 (27.9%)
Reasonably confident	30 (20.4%)
More confident	7 (4.8%)
Monitoring cross-sex hormone therapy	
Not at all confident	56 (38.1%)
Less confident	52 (35.4%)
Reasonably confident	31 (21.1%)
More confident	7 (4.8%)

TABLE 3 Levels of training

Training in transgender medicine as a:	Medical student Number (%)	Endocrine trainee. Number (%)	Qualified endocrinologist Number (%)
Yes	2 (1.4%)	53 (36.1%)	43 (29.3%)
No	136 (92.5%)	85 (57.8%)	59 (40.1%)
N/A	3 (2.0%)	3 (2.0%)	39 (26.5%)
No answer given	6 (4.1%)	6 (4.1%)	6 (4.1%)
Characteristic			**Number (%)**
Amount of training received in transgender medicine			
Too much			0 (0.0%)
Adequate			18 (12.2%)
Not enough			129 (87.8%)
Desire for more training in treating TGD individuals			
Yes			133 (90.5%)
No			14 (9.5%)
Whether relevant Endocrine Society clinical practice guidelines had been read			
Yes			68 (46.3%)
No			79 (53.7%)

not feel confident prescribing hormone therapy and opted to refer to a colleague or gender service. Only 19% felt comfortable treating. The large majority (75%) felt less confident or not at all confident in commencing hormone therapy in a TGD patient compared to other areas of endocrinology. On the other hand, almost half (46%) felt reasonably or more confident in performing a history. Data are summarized in Table 2.

To determine whether any previous clinical experience with transgender individuals is associated with a higher level of confidence, Cochran-Armitage test was conducted to compare the confidence levels of practitioners who had seen one or more transgender patient compared to those who had seen none. There was a statistically significant difference in all aspects including performing a consultation, history taking, commencing hormone therapy and monitoring of hormone therapy with higher levels of confidence in those who had previously seen a TGD patient ($P < .0001$). Additionally, there was a significantly higher level of confidence in all areas in those who had previously read the Endocrine Society guidelines in this area ($P < .0001$) (see Appendix 2).

3.3 | Training and experience

A very low proportion (1%) reported having received had any training in transgender health as a medical student. In addition, 36% reported receiving training in transgender health during their endocrinology advanced training and 29% received some training since qualifying as an endocrinologist. Overall, 88% believed there was not enough training in transgender medicine and 91% desired more training. Over half (53.7%) had never read international guidelines. Data are summarized in Table 3.

4 | DISCUSSION

This is the only study to assess adequacy of training of endocrinologists in managing TGD individuals in Australia, and, more specifically, to assess if the clinical experience of having seen a TGD patient or reading clinical guidelines was associated with higher clinician confidence in providing gender-affirming care. In this national survey involving 147 adult endocrinologists and trainees, we found that firstly, clinicians lacked confidence when prescribing and monitoring hormone therapy; secondly, there was a widespread lack of training in transgender medicine from student to postgraduate levels; and thirdly, endocrinologists desired further education and training. We also demonstrate that clinical experience with one or more TGD patients and familiarity with the US Endocrine Society guidelines were both associated with improved confidence to provide gender-affirming care.

4.1 | Levels of confidence

Whilst our survey differed to those used in other studies, our data suggest that confidence levels of Australian endocrinologists in managing transgender individuals were even lower than their overseas counterparts. A survey of US endocrine conference attendees found that 41% felt 'somewhat' or 'very' competent to provide transgender care.[19] This compares to 33% of people in our study that felt at least reasonably confident compared to other areas of endocrinology.

In this study, clinical experience and awareness of published guidelines were both associated with higher levels of confidence and should therefore be the target of future educational interventions. It

is important to remember that confidence does not always translate to competence. Assessing competence would be important aspect to address in future studies.

4.2 | Training and experience

Our findings show that less than one in five Australian endocrinologists and trainees who responded felt they had received sufficient training with respect to initiating therapy, and more than half preferred to refer TGD individuals to a colleague. The majority (88%) believed they had not received enough training in transgender medicine but despite this over 85% have managed at least one TGD patient. These findings are similar to a survey of over 400 US Endocrine Society members, which found that over 80% had never received training in the care of TGD patients even though almost 80% had treated a TGD patient.[18] Similarly, low levels of training were reported in other specialties relevant to the TGD community such as US plastic surgery and urology residency programmes.[22] In this study, only 36% had ever seen five or more TGD patients at any stage and less than 12% currently had five or more TGD individuals under their care. Adequate clinical exposure is an important as those who had seen one or more TGD individual also had higher levels of confidence in this area.

A likely explanation for the lack of training in TGD health in medical schools and endocrinology training programmes is a delay in these institutions responding to changes in clinical care needs. Although TGD individuals have always been part of our society, the growing awareness and increasing visibility of the community has brought the issues they face to the forefront. Adapting the teaching agenda of medical schools and fellowship programmes takes time, and there is lag between identifying an area where more education is needed and implementing practical changes to address it. Dubin et al postulate that a lack of well-established best practice guidelines, barriers to implementing any additional material to an already busy medical school curricula and lack of evidence to guide the best way to implement these changes all contribute.[23]

Additionally, a 2017 US survey of endocrinology fellowship programme directors revealed there was a perceived a lack of faculty interest or experience in transgender health care as well as lack of training resources and lack of funding for this area.[18] Our findings lend support to the urgent need to address training gaps which could be targeted through expected clinical exposure to TGD patients as part of endocrine training.

4.3 | Further education

Further training was desired by 91% of our participants. In addition to implementing changes to medical school curricula, development of a transgender education programme specifically targeted to endocrinology trainees could address the specific training and confidence shortfalls uncovered by this study. A 2018 US survey of endocrinology trainees found that lectures from visiting professors were the most preferred method of receiving transgender healthcare content.[24] When asked to rate their comfort level before and after an educational session 73% of US participants felt a single session improved their comfort level with transgender care and 91% felt a similar session should be mandatory in endocrinology training programmes.[24] Other desired methods of education included elective rotations, online training modules and attendance at meetings.[24]

This study showed higher levels of confidence in those who had some clinical experience in TGD health care. There are many avenues for exposure of endocrinologists and endocrine trainees to TGD patients. Establishing dedicated gender clinics are one option which would not only help to address the shortfall in services for TGD individuals but also allow focused training rotations for endocrinology trainees to gain valuable practical experience.[24] An alternative option to manage the rapidly increasing numbers of TGD people seeking gender-affirming hormone therapy is to consider TGD endocrine care as mainstream endocrinology. Given that management principles with testosterone and estradiol are similar to treatment of hypogonadism from other causes such as menopause, this is a feasible approach.

It is also important to consider that educating all doctors, not just endocrinologists, will have far-reaching benefits. TGD individuals, like everyone, experience general health concerns. A person's health needs may depend on their anatomy rather than their gender identity, such as cervical screening in TGD people assigned female at birth and prostate screening in TGD people assigned male at birth. Practical changes such as adapting patient registration forms to include gender options beyond the binary, using the person's preferred name and pronoun, as well as availability of appropriate non-gendered toilet facilities are also important.[25]

Just over half of current endocrinologists and trainees surveyed had never read the relevant international guidelines, and they also had lower levels of confidence in TGD health care. However, international guidelines do not address local differences in practice and availability of specific medications. For example, the antiandrogen agent cyproterone acetate is not approved by the US FDA due to case reports of hepatotoxicity, yet it is widely used in Europe, Australia and elsewhere. Conversely, spironolactone is almost never used as an antiandrogen agent in Europe but is commonly used in United States and Australia. This provides an impetus for the development of locally relevant resources, and in response to findings from this survey, we have published Australian-based treatment recommendations for gender-affirming hormonal therapy.[26]

4.4 | Limitations

The sample size was relatively small with 27% of Endocrine Society of Australia members taking part in this study. However, this is much higher than a similar US study where the response rate was under 6%[18] and higher than other comparable studies.[21] Responder bias is a consideration with a predominance responders from the

south-eastern states, although the majority of endocrinologists and trainees are based in these areas. There were few participants from Northern Territory, Australian Capital Territory and Tasmania, reflecting the fewer practicing endocrinologists and trainees in these areas. It is postulated that nonresponders may be even less engaged. Nonetheless, our results mirror those identified overseas.[18-20] The survey was advertised at national endocrinology training events, which may explain the large number of responses from advanced trainees. Paediatric endocrinologists are under-represented in this cohort however the Endocrine Society of Australia is comprised of predominantly adult endocrinologists and trainees.

4.5 | Implications and future direction

Based on our findings we recommend the following:

1. Incorporation of TGD health into medical school and endocrine training curricula. Training or lectures delivered should be designed by experienced clinicians in collaboration with TGD community members. Inclusion of community voices allows an understanding of health issues and barriers faced by the TGD community and the importance of respect and affirmation with nongendered inclusive language, which is as important as the specifics of gender-affirming hormonal therapy.
2. Clinical exposure of all endocrine trainees to TGD patients during their training programme.
3. Improved visibility of TGD health and research at professional society conferences and seminars to upskill endocrinologists.
4. Promotion of existing local or international guidelines on the endocrine and related care of TGD people to trainees and endocrinologists.
5. Further research to assess the impact of educational interventions to ensure knowledge, confidence and competence in TGD medicine increases over time.

4.6 | Conclusions

Whilst TGD community members express an inability to find doctors willing to provide gender-affirming hormone therapy as a major barrier to health care, our study suggests that this may be related to a widespread lack of training and a lack of confidence amongst Australian endocrinologists and trainees in the provision of gender-affirming hormone therapy. An Australian position statement on the treatment of transgender and gender diverse people has been developed in response to the strong desire for increased training. In addition, a co-ordinated response from endocrine societies, fellowship programme directors, training providers, healthcare educators and universities in partnership with TGD community members is urgently needed to ensure endocrinologists are confident and competent in being able to provide necessary care for TGD people.

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CONFLICT OF INTEREST

The authors have no conflicts to declare.

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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APPENDIX 1

Transgender Care Survey: Endocrinologists and Trainees

The purpose of this study

This survey is to help us understand aspects of transgender healthcare and the levels of educations and training for Endocrinologists and Trainees.

Taking part in this study

You must be aged over 18 to take part in this survey. By completing the following survey, you are telling us that understand the purpose of this study, and that results will be used for research purposes. If you do not wish to take part in this project, please do not fill out the survey. All responses are anonymous.

Further information and who to contact

The person you may need to contact will depend on the nature of your query.

Clinical contact person: Dr Ingrid Bretherton PhD Candidate

Telephone 9496 2486

Email ibretherton@student.unimelb.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Complaints contact person

Complaints Officer (03) 9496 4090 or (03) 9496 3248 Email ethics@austin.org.au

Q1 What is your gender?

□ Male
□ Female
□ Other (please specify)

Q2 What is your age range?

□ 20-29
□ 30-39
□ 40-49
□ 50-59
□ 60-69
□ >70

Q3. Which Australian State do you live in?
□ Australian Capital Territory
□ New South Wales
□ Northern Territory
□ Queensland
□ South Australia
□ Tasmania
□ Victoria
□ Western Australia

Q4. What is your occupation?
□ Adult Endocrinologist
□ Paediatric Endocrinologist
□ Advanced Trainee in Endocrinology
□ Other (please specify)

Q5. Where is your main place of practice? (where you work the most hours during the week)
□ Tertiary hospital
□ Hospital - non-tertiary Private clinic
□ Other (please specify)

For the following questions, formal training refers to lectures, tutorials, conference presentations or workshops etc

Q6. Have you ever attended any training in transgender medicine as a
Medical Student?
□ Yes
□ No
□ N/A

Endocrinology Advanced Trainee or Medical Officer?
If you are still training, have you received any training to date (excluding today's lecture)?
□ Yes
□ No
□ N/A

Qualified Endocrinologist?
□ Yes
□ No
□ N/A

Q7. Overall, how would you rate the amount of training you received in transgender medicine?
□ Too much
□ Adequate
□ Not enough

Q8. Would you like to receive more training in treating trans and gender diverse individuals?
□ No
□ Yes

If yes, how would you prefer this to be delivered? Seminar or Symposium at Conference, Dedicated series of lectures on transgender health, Dinner/Lunch Meeting, Online Resources, Clinical Observation, Peer support groups

Q9. How many trans or gender diverse individuals have you ever seen?
□ None
□ 1-4
□ 5-9
□ 10-19
□ >20

Q10. How many trans or gender diverse individuals are currently under your care?
□ None
□ 1-4
□ 5-9
□ 10-19
□ >20

Q11. Have you ever read the Endocrine Society clinical practice guidelines on treatment of transsexual individuals?
□ Yes
□ No

Q12. Please consider this scenario. You receive a referral from a GP to treat a 30-year-old birth assigned female who identifies as male and has been formally diagnosed with gender dysphoria by an experienced psychiatrist. They are now seeking testosterone as cross-sex hormone therapy. Would you
□ Prefer not to treat
□ Refer to a colleague or specialist gender service Consider treating
□ Feel comfortable treating
□ Unsure
□ Not applicable - I am a paediatric endocrinologist

Q13. Compared with other areas in Endocrinology, how confident do you feel with the various medical aspects of managing trans and gender diverse patients?

	Not at all confident	Less confident	Reasonably confident/the same	More confident
Performing a consultation with a trans or gender diverse individual				
Taking a history from a trans or gender diverse individual				
Commencing cross-sex hormone therapy				
Monitoring cross-sex hormone therapy				

*Q14. Would you find an online resource with Australian-based evidence-based resources beneficial? This would be aimed at assisting endocrinologists, GPs and other health professionals to treat individuals with gender dysphoria including suggested management of hormonal therapies, lists of surgeons, legal resources, available gender clinics etc
□ Yes
□ No
□ Somewhat
□ Unsure
*Q15. What other areas (if any) of managing trans or gender diverse individuals would you like training in?
*Q16. Do you have any other comments?
Thank you very much for your responses.
*Questions with few responses or requiring free text answers excluded from analysis

APPENDIX 2

TABLE A1 Comparison of confidence levels of practitioners when performing a consultation (question 13) who had seen one or more transgender patient compared to those who had seen none (question 9) using Cochran-Armitage test

Aspect of consultation	No. TGD individuals ever seen	Not at all confident. No. (%)	Less confident. No. (%)	Reasonably confident/the same. No. (%)	More confident. No. (%)	Total
Performing a consultation with a trans or gender diverse individual	None	10 (48.6%)	10 (47.6%)	1 (4.8%)	0 (0.0%)	21
	≥1	27 (21.4%)	52 (41.3%)	41 (32.5%)	6 (4.8%)	126
	Total	37 (25.2%)	62 (42.2%)	42 (28.6%)	6 (4.1%)	147
					P-value	.0012
Taking a history from a trans or gender diverse individual	None	6 (30.0%)	11 (55.0%)	3 (15.0%)	0 (0.0%)	20
	≥1	14 (11.1%)	46 (36.5%)	58 (46.0%)	8 (6.4%)	126
	Total	20 (13.7%)	57 (39.0%)	61 (41.8%)	8 (5.5%)	146
					P-value	.0010
Commencing cross-sex hormone therapy	None	18 (85.7%)	3 (14.3%)	0 (0.0%)	0 (0.0%)	21
	≥1	51 (40.5%)	18 (30.2%)	30 (23.8%)	7 (5.6%)	126
	Total	69 (46.9%)	41 (27.9%)	30 (20.4%)	7 (4.8%)	147
					P-value	.0002
Monitoring cross-sex hormone therapy	None	17 (81.0%)	3 (14.3%)	1 (4.8%)	0 (0.0%)	21
	≥1	39 (31.2%)	49 (39.2%)	30 (24.0%)	7 (5.6%)	125
	Total	56 (38.4%)	52 (35.6%)	31 (21.2%)	7 (4.8%)	146
					P-value	.0001

TABLE A2 Comparison of confidence levels of practitioners when performing a consultation (question 13) who had seen one or more transgender patient compared to those who had seen none (question 9) displayed as column wise percentages

Aspect of consultation	No. TGD individuals ever seen	Not at all confident	Less confident	Reasonably confident/ the same	More confident
Performing a consultation with a trans or gender diverse individual	None	27.0%	16.1%	2.4%	0.0%
	≥1	73.0%	83.9%	97.6%	100.0%
Taking a history from a trans or gender diverse individual	None	30.0%	19.3%	4.9%	0.0%
	≥1	70.0%	80.7%	95.1%	100.0%
Commencing cross-sex hormone therapy	None	26.1%	7.3%	0.0%	0.0%
	≥1	73.9%	92.7%	100.0%	100.0%
Monitoring cross-sex hormone therapy	None	30.4%	5.8%	3.2%	0.0%
	≥1	69.6%	94.2%	96.8%	100.0%

TABLE A3 Comparison of confidence levels of practitioners when performing a consultation (question 13 in those who has previously read the relevant Endocrine society guidelines to those who had never read them (question 11) using Cochran-Armitage test

Aspect of consultation	No. TGD individuals ever seen	Not at all confident. No. (%)	Less confident. No. (%)	Reasonably confident/the same. No. (%)	More confident. No. (%)	Total
Performing a consultation with a trans or gender diverse individual	None	30 (38.0%)	36 (45.6%)	12 (15.2%)	2 (1.3%)	79
	≥1	7 (10.3%)	26 (38.2%)	30 (44.1%)	6 (7.4%)	68
	Total	37 (25.2%)	62 (42.2%)	42 (28.6%)	8 (4.1%)	147
					P-value	<.0001
Taking a history from a trans or gender diverse individual	None	16 (20.5%)	40 (51.3%)	20 (25.6%)	2 (2.6%)	78
	≥1	4 (5.9%)	17 (25.0%)	41 (60.3%)	6 (8.8%)	68
	Total	20 (13.7%)	57 (39.0%)	61 (41.8%)	8 (5.5%)	146
					P-value	<.0001
Commencing cross-sex hormone therapy	None	51 (64.6%)	22 (27.9%)	5 (6.3%)	1 (1.3%)	79
	≥1	18 (26.5%)	19 (27.9%)	25 (36.8%)	6 (8.8%)	68
	Total	69 (46.9%)	41 (27.9%)	30 (20.4%)	7 (4.8%)	147
					P-value	<.0001
Monitoring cross-sex hormone therapy	None	44 (56.4%)	26 (33.3%)	7 (9.0%)	1 (1.3%)	78
	≥1	12 (17.6%)	26 (38.3%)	24 (35.3%)	6 (8.8%)	68
	Total	56 (38.4%)	52 (35.6%)	31 (21.2%)	7 (4.8%)	146
					P-value	<.0001

TABLE A4 Comparison of confidence levels of practitioners when performing a consultation (question 13 in those who had previously read the relevant Endocrine society guidelines to those who had never read them (question 11) displayed as column-wise percentages

Aspect of consultation	No. TGD individuals ever seen	Not at all confident	Less confident	Reasonably confident/ the same	More confident
Performing a consultation with a trans or gender diverse individual	None	81.1%	58.1%	28.6%	16.7%
	≥1	18.9%	41.9%	71.4%	83.3%
Taking a history from a trans or gender diverse individual	None	80.0%	70.2%	32.8%	25.0%
	≥1	20.0%	29.8%	67.2%	75.0%
Commencing cross-sex hormone therapy	None	73.9%	53.7%	16.7%	14.3%
	≥1	26.1%	46.3%	83.3%	85.7%
Monitoring cross-sex hormone therapy	None	78.6%	50.0%	22.6%	14.3%
	≥1	21.4%	50.0%	77.4%	85.7%

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Health Needs of Trans and Gender Diverse Adults in Australia: A Qualitative Analysis of a National Community Survey

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Abstract: There is an increasing demand for trans and gender diverse (TGD) health services worldwide. Given the unique and diverse healthcare needs of the TGD community, best practice TGD health services should be community-led. We aimed to understand the healthcare needs of a broad group of TGD Australians, how health professionals could better support TGD people, and gain an understanding of TGD-related research priorities. An anonymous online survey received 928 eligible responses from TGD Australian adults. This paper focuses on three questions out of that survey that allowed for free-text responses. The data were qualitatively coded, and overarching themes were identified for each question. Better training for healthcare professionals and more accessible transgender healthcare were the most commonly reported healthcare needs of participants. Findings highlight a pressing need for better training for healthcare professionals in transgender healthcare. In order to meet the demand for TGD health services, more gender services are needed, and in time, mainstreaming health services in primary care will likely improve accessibility. Evaluation of training strategies and further research into optimal models of TGD care are needed; however, until further data is available, views of the TGD community should guide research priorities and the TGD health service delivery.

Keywords: transgender persons; gender identity; health services; health services needs and demand; health services for transgender persons

1. Introduction

With increasing visibility of trans and gender diverse (TGD) people and increasing demand for TGD health services worldwide [1,2], attempts are being made to design appropriate health services. Correspondingly, there has been an exponential rise in the number of research studies published in TGD health [3]. The TGD community has unique and diverse healthcare needs that are frequently coupled with societal discrimination and stigma, which may impact upon the trust of health professionals as well as overall health and well-being.

Best practice TGD health services should be community-led and co-designed with the TGD community [4]. Previous small surveys have suggested that increased education of medical practitioners was needed to better engage with gender diverse clients [5]. However, the TGD community is diverse, and small, focused consumer advisory groups may not necessarily capture the views of the broader

community. In order to guide policy direction, the design of health services and relevant research areas for the TGD community, we aimed to understand the healthcare needs of a broad group of TGD Australians, how health professionals could better care and support TGD people and gain an understanding of community views on TGD-related medical research priorities.

2. Materials and Methods

This anonymous online survey of TGD Australian adults was designed to provide a platform for the TGD community to voice their healthcare needs and priorities. Purposeful, criterion-specific sampling was used to recruit from this minority population. Inclusion criteria were assessed via three screening questions: a) resident of Australia; b) identification as trans or gender diverse or had previously identified as such in the past; c) aged over 18 years.

Participants were recruited for the survey through a post on the Trans Medical Research Facebook page. This post was shared by 275 individuals and online transgender support groups. The survey was also promoted at several LGBTIQA+ events in Sydney and Melbourne, Australia. The survey remained anonymous and as such, written informed consent was not obtained; however, continuation with the survey implied informed consent. Individuals were eligible to complete the survey on one occasion only, and duplicate responses from the same Internet Protocol (IP) address were excluded.

The study was approved by the Austin Health Human Research and Ethics Committee (HREC/17/Austin/372). The online platform SurveyMonkey (SurveyMonkey Inc. San Mateo, California, USA) was used to design and collect responses to the survey. The survey was available online to respondents between 1st September 2017 and 31st January 2018. Questions in the survey covered sociodemographic and clinical data and participants were asked to report past medical diagnoses of various conditions and access to various types of health care providers were determined (reported elsewhere). This paper selected three questions out of the collected data set, which allowed for open free-text responses for qualitative analysis. These were; 1) How do you think healthcare professionals can better support you? 2) What do you think are the two most important issues for your health, i.e., if you could improve your health right now, what would you do? 3) Are there any areas of trans-related medical research that you would like addressed?

The responses from all participants to each of the three survey questions were collated into three data transcripts. One of the researchers (AW) coded the participant responses one-by-one using NVivo qualitative data analysis software version 12 (QSR International Pty Ltd., Doncaster, Australia). Codes were developed from the data during the coding process (i.e., codes were not previously established). A second researcher (SZ) then independently coded the data against these codes and queries and discrepancies in the interpretation of the codes were discussed and resolved. Using NVivo, a coding comparison query was performed to determine the degree of agreement between the two coders. This comparison calculated a Cohen's Kappa value for each code's content. The average Cohen's Kappa value across the different codes for each survey question was calculated, with each code given equal weight.

3. Results

A total of 964 responses to the survey were obtained; however, after excluding participants who did not identify as trans or gender diverse, those not living in Australia, and duplicate responses, there was a total of 928 eligible responses to the survey. For the three questions of focus in this analysis, 763 responses were received for questions 1 and 2, ("How do you think healthcare professionals can better support you?" and "What do you think are the two most important issues for your health, i.e., if you could improve your health right now, what would you do?") and 641 responses were received for question 3 ("Are there any areas of trans-related medical research that you would like addressed?").

Responses were received from all States and Territories in Australia. In brief, 56% of respondents were birth-assigned females, 43% birth-assigned males, and 1% stated they were intersex. A total of 37% identified as trans female, trans feminine, trans woman or female, 36% identified as trans male,

trans masculine, trans man or male, and 27% had non-binary gender identities. The median age of participants was 28 (IQR 23–39). Participants were generally well-engaged with the Australian health care system, with 80% having a regular primary care doctor.

The data from the first question "How do you think healthcare professionals can better support you?" was encoded to 7 codes, which were then separated into two overarching themes; "Provide Accessible Healthcare" and "Training and Professional Development" (see Table 1). The average level of agreement between the two coders, across all codes for the first question, was high, with an average Kappa coefficient of 0.74.

Table 1. Codebook for survey question: How do you think healthcare professionals can better support you?

Theme	Code
Provide Accessible Care	Improve accessibility to healthcare Information for the community
Training and Professional Development	Training for medical professionals Professional development Communication with the community Need for more guidelines, research, advocacy Positive experiences

The data from the second question "What do you think are the two most important issues for your health, i.e., if you could improve your health right now, what would you do?" was encoded to 11 codes. Ten of the codes were separated into three overarching themes; "Accessibility and Training for Healthcare Professionals", "Trans-related medical intervention", and "Health, Wellbeing and Support" (see Table 2). One of the codes included neutral and unclassifiable responses and was not included under any of the themes (1.7% of responses). The average level of agreement between the two coders, across all codes for the second question, was high, with an average Kappa coefficient of 0.89.

Table 2. Codebook for survey question: What do you think are the two most important issues for your health, i.e., if you could improve your health right now, what would you do?

Theme	Code
Accessibility and Training for Healthcare Professionals	Accessibility issues Educate health professionals Community building, information for the community
Transgender-related medical intervention	Trans and related medical intervention
Health, Wellbeing and Support	General well-being Housing, employment, family issues Less social discrimination, more social or community support Mental well-being Other medical issues Substance use

For the third question, "Are there any areas of trans-related medical research that you would like addressed?", the data were encoded to 10 codes. Nine of the codes were separated into three overarching themes; "Trans Medical Advancements", "Accessibility and Standards of Care", and "Greater Breadth of Research and Understanding" (see Table 3). One of the codes included responses such as "don't know" and "nothing" and was not included under any of the themes (15.7%). The average level of agreement between the two coders, across all codes for the third question, was high, with an average Kappa coefficient of 0.89.

Table 3. Codebook for survey question: Are there any areas of trans-related medical research that you would like addressed?

Theme	Code
Trans Medical Advancements	Surgical techniques Potential associated health issues Hormone effects and risks Alternative and associated treatment
Accessibility and Standards of Care	Accessibility Diagnosis or treatment guidelines Community support and communication
Greater Breadth of Research and Understanding	Adolescent issues Adult trans research Aged care All or others Mental health, Potential Neurodiversity association

3.1. Support Required from Healthcare Professionals: Question 1 "How do You Think Healthcare Professionals can Better Support You?"

3.1.1. Theme 1: Training and Professional Development for Health Professionals

Almost half of participants (44.8%) indicated that knowledge around transgender issues is generally lacking and that greater training of medical professionals around TGD health issues is paramount.

> *General knowledge of trans* patient care and the medical needs/concerns of transgender patients seems to be extremely lacking amongst doctors. More education is needed.*

> *Healthcare professionals need to access education on gender identity. The biggest barriers at the moment are misunderstanding and lack of knowledge.*

> *From previous experiences I think better education regarding gender diverse healthcare is needed. Ideally it would start in medical school.*

The lack of knowledge meant that many TGD people felt that to have their healthcare needs met, they had to attend a specialist doctor or clinic, which often came with long wait times for appointments and high costs.

> *Better education. I have to go to an LGBT clinic just because GPs are ignorant.*

> *More awareness of trans issues and treatments. Currently only doctors and surgeons with proven experience in treating trans patients seem to know what to do with us.*

Correspondingly, in addition to an increase in training, just over one in five of the participants (21.4%) reported improvements in professionalism as key. Three main issues around professionalism were raised by participants: the use of correct name and pronouns; inappropriate and irrelevant questions about their transgender experience, and incorrect focus on their TGD status as a cause of any presenting mental and medical health issues.

> *Not assume my gender, not laugh at me when I say I need a certain type of medical care, not ask me questions about my transgender experience/status that is irrelevant to the current concern/procedure, ask me my pronouns, use them correctly.*

> *If they could stop being convinced that being trans means that my unrelated physical disability is actually just me being crazy/anxious/depressed/psychotic/malingering, that would be excellent. I want my healthcare professionals to use my correct name and pronouns above everything else. They don't need to address my trans identity unless it is directly relevant to whatever I am seeing them for.*

Other responses to the question "*How do you think healthcare professionals can better support you?*" included provision of reliable health information such as treatment pathways, greater communication with the TGD community as well as a desire for more guidelines, research, and advocacy.

> *Flag somehow that they are trans-friendly/queer-friendly, for example, with a note on their website or a sign or sticker, that would be really helpful in helping me figure out which healthcare professionals are safe.*

> *Ideally healthcare professionals will let the patient lead the discussion regarding what they need. For example, not forcing a trans* person to follow any one medical path for transition.*

> *All registered GP's should be sent a pamphlet on the current laws and literature about trans people. And the pathway that they can help their trans patient get onto, hormones, surgery, etc.*

Less than 5% of the participants responded to this question, by reporting they had only had positive experiences with healthcare professionals. A willingness to listen, learn, and respect a person's name and pronouns were sited as integral to feeling supported.

> *I am lucky to have a number of GPs at the clinic I attend who are very supportive of patient-led care and who go out of their way to ensure any additional practitioners I see will be trans-friendly. I wish all healthcare professionals would do this.*

> *A willingness to try and understand the thoughts and feels we go through when they haven't encountered a trans person before. My current healthcare professionals have done this for me and that has made me stop seeing others to see them.*

3.1.2. Theme 2: Provide Accessible Care

Improving the accessibility of medical interventions to aid gender transition was a major theme of responses to how health professionals could assist TGD people. An integral issue reported was 'gatekeeping'; referencing a need to undertake multiple psychiatric assessments in order to be deemed suitable for hormone treatments or surgery, which often delayed treatment and negatively impacted mental health.

> *I've only ever been hurt by these gatekeepers. They have never saved me from a mistake, they have only gotten in my way, delayed access to important interventions, and sometimes abusing their total monopoly over my access to health care*

> *Stop being hate keepers, making us prove ourselves and meeting your notions of trans and who is deserving of support. Instead, collaborate with us and support us in our health and well being aspirations.*

Out-of-pocket expenses for treatments, particularly gender-affirming surgery, was frequently reported to be prohibitive, yet such treatments were described as vital to improve mental and general wellbeing.

> *I think the access to and cost to trans healthcare should be within reach of all trans Australians.*

> *Make it more cost effective. Most of us need to get loans or tap into super to pay for surgery and that puts a lot of monetary pressure onto us at a time when we're at our most vulnerable.*

> *Help to make surgery be more affordable. I really want to have genital surgery with the rod implant. But with a price over $90000 that's not really possible for your average person. Its not just a cosmetic procedure as they say. It is mentally affecting my life in a big way.*

Long wait times and geographical accessibility were also raised as issues to be addressed by healthcare professionals, as well as the lack of availability of certain treatments in Australia.

Have more professionals who specialise in the area so wait times aren't so long.

Easier access to support. I shouldnt have to travel to a capital city to get gender support.

Better pathways towards gender confirming surgeries provided within this country instead of forcing folks to seek the help they NEED outside of the country and putting themselves at risk to do so.

3.2. Self-Perceived Health Issues: Question 2 "What do You Think are the Two Most Important Issues for Your Health, i.e., If You Could Improve Your Health Right Now, What Would You Do?"

3.2.1. Theme 1: Trans and Related Medical Intervention

Transgender related medical interventions were reported to be highly important to the healthcare needs of over one third (36%) of the transgender participants. Specifically, the most common interventions included a range of surgeries, post-surgery support, hormone replacement therapy, speech training, and hair removal.

Top surgery for better confidence and all-round positive outlook on life.

Better post operative support regardless of where you had surgery.

Chest/respiratory and back pain issues from long-term binding that has caused damage to my chest and back. I would need top survey ASAP to stop the damage but the waiting list is over a year long, but then my chest could become even more damaged.

3.2.2. Theme 2: Mental and General Wellbeing

General wellbeing was reported as a key healthcare need by about one third (32.2%) of the participants. This included quality of sleep, exercise and fitness, and a healthier diet.

Get more sleep and better sleep.

Access to post-transition support eg fitness and health (eating disorders and weight gain).

Some participants reported barriers to achieving their general wellbeing needs, such as difficulty finding dieticians and exercising environments that are affirming and not discriminatory against TGD people.

Find a place I feel comfortable exercising; public gyms are intimidating due to my trans status.

Be able to find exercise classes that are run by or for LGBT people so I feel comfortable and not worse about myself.

Mental wellbeing concerns were raised as an important healthcare need by almost one-third of participants (31.6%). This included several references to self-harm and suicidal ideation, and a desire to reduce stress, depression, anxiety and other mental health issues, in order to gain a more positive outlook on life.

Self-harm and almost constant suicidal thoughts.

How to deal with stress, which in general would help me with anxiety and dysphoria also.

Having access to affordable mental health professionals, with training and experience with TGD people was also reported as a self-perceived health issue.

Accessible psychological support. Currently psychs (more so for specialist trans care) are unavailable or are inaccessible for price.

Regular support from a trained, knowledgable psychologist, not just limited to the few sessions via a mental health plan.

Additionally, 15.1% of participants reported that other medical issues, such as chronic pain, were of key importance. Other self-perceived health issues included a need to reduce social discrimination of transgender people, an increase in social support, housing, employment and family issues, and addressing substance use.

Broader understanding and acceptance of tran speople in the general community would make my mental and physical health improve tremendously.

My fear of other people in public places and lack of understanding by others has a huge effect on my anxiety and depression.

Change jobs to somewhere I could be open about my gender identity to improve my mental health.

3.2.3. Theme 3: Accessibility and Education

Aligned with responses to necessary support required from health professionals, almost one in four participants (22.5%) reported that access to gender-affirming healthcare was one of their most important health issues, including 'gatekeeping', the lack of financially accessible specialists, mental health support, and access to gender-affirming medical interventions.

Surgery (top surgery) would greatly improve both my physical and mental health, however, cost makes this inaccessible.

Access a speech pathologist (currently prohibitively expensive); switch from Spironolactone to GnRH analogues (also prohibitively expensive).

Access to a psychologist who is fully skilled, aware, and trained to understand both my identities as a nonbinary and demisexual person, as well as fully covered financially.

In terms of more generalised access to healthcare as a transgender person, discrimination was seen as a central health issue.

Be able to access medical and psychological services without discrimination, harassment, verbal abuse, or be refused care because I'm trans.

Like with the first survey question, education for health professionals around transgender experiences and transgender healthcare was reported as a priority. Other keys issues included a desire for greater community building and information for the TGD community, with a number of participants describing difficulting finding trans-related healthcare information.

Better access to reliable information about what services are available and where to find them.

I want to get on hormone therapy but literally have no idea how and who to ask.

3.3. Trans-Related Medical Research Topics: Question 3 "Are There Any Areas of Trans-Related Medical Research That You Would Like Addressed?"

3.3.1. Theme 1: Medical Advancements

Over a quarter of participants (27%) indicated that hormone effects and risks was an important area of TGD medical research.

I think there should be more research on the long-term effects of hormone treatment and whether there are any risks involved in taking hormones (e.g., increased risk for some cancers).

I'd also like to know more about the long term risks of testosterone. Do I need a hysterectomy after 5 years? How many of my health issues can be explained by being on testosterone for 6 years?

Greater research into gender-affirming surgical techniques was desired by 18.7% of participants. In particular, improvements in bottom surgery techniques and availability were commonly mentioned.

Australia could do well to increase the training and quality of the surgeons able to provide gender confirming surgeries. Internationally we have seen advancement in trans healthcare that is not being reflected here.

Bottom surgery for trans men is inadequate and highly dangerous, more research and improvements need to be done.

In addition, 6.2% of participants indicated that potential health issues associated with transgender interventions, such as chest binding and genital tucking is an important area of research, while there was also interest in alternative and associated transgender treatments, such as more effective hair removal.

3.3.2. Theme 2: Accessibility and Standards of Care

Access to gender-affirming healthcare was indicated as an important area of research by 10% of participants. This included research into more cost-effective medical interventions and research into better standards of care. Other research areas of community interest included research into diagnosis or treatment guidelines, community support, communication, and the impact of social support on health outcomes in transgender people and the need for more transgender people to conduct research.

WHAT the options are for transitioning. I STILL can't find anything definitive.

Better guides for how to prescribe hormones.

3.3.3. Theme 3: Greater Breadth of Research and Understanding

Mental health and neurological indicators were areas of research desired by 15.3% of participants. This included exploration of the correlation between autism spectrum and gender diversity and neurological or other biological indicators for identifying and validating transgender people.

Correlation between autism spectrum disorders and transgender identity.

Further understanding its causes would likely provide greater acceptance in the community so people including trans people can understand and accept that gender identity doesn't always align with genitals from an early age. I really wish I knew what made me trans it would have made it easier to accept in myself and help my siblings and parent accept me better.

There were several other research areas desired including non-binary identities and experiences, adolescent issues, aged care and intersex conditions.

Non binary people, please!! We get forgotten and erased so much.

I think there should be more research on the amount of trans people with eating disorders, because in my experience it's unfortunately common.

More research into puberty blockers affects on development to hopefully get rid of some of the stigma and hesitance around its use.

Impacts and experiences of stigma, discrimination and also affirmative care and supportive environments.

Some participants indicated that there should be transgender research across all areas of being TGD.

Research is totally lacking. I think we're ignored as a population. The healthcare offered doesn't seem to be based on good evidence and it's like we're medical research subjects undergoing experimental treatment. Nobody knows what they're doing.

4. Discussion

This large qualitative survey provides an in-depth insight into health and research issues of most concern for the Australian TGD community. A need for better training for healthcare professionals in TGD health and providing ready access to hormonal, surgical, and psychological support to aid gender transition for optimal mental and general well-being were the most commonly reported healthcare needs of TGD people.

Whilst Australia has one of the world's best health systems that provides universal government-funded healthcare in parallel with the private sector [6], there remain many shortcomings. Our findings suggest that TGD health is one area in need of policy direction and resourcing to best support this marginalised community. Basic requirements, including feeling safe and validated, are not being met. Consistent with previous research [5,7–11], transgender participants in this study frequently indicated that current knowledge, experience, and professionalism amongst healthcare professionals around transgender health is poor and that there is a pressing need for better training for health professionals and more research in transgender healthcare. This includes training regarding using the correct name and pronouns, which has been shown to be vitally important in validating TGD experiences [10,12–14]. It can be argued that training programs in transgender healthcare would not only improve knowledge and professionalism and reduce discrimination but would address in part, the issue of lack of access to health services and inability to find doctors to provide gender-affirming treatments [15,16].

Training for all clinicians and patient-facing health professionals, including emergency departments and administration and clerical staff, are very much required, and professional societies need to place TGD health as a training priority [10,14,17]. Moreover, more investment in training programs nationally is very much needed, as well as the implementation of trans cultural awareness amongst various health professional degrees and accreditations. This is not limited to Australia—in a US survey of over 400 practising clinicians, 80% indicated that they had never received training regarding the care of TGD patients even though almost 80% have treated a TGD patient [18].

Ability to access and obtain trans and related medical interventions is undoubtedly of major importance to allow an individual's physical characteristics to align with their gender identity. Accessibility is, however, an ongoing and prevalent issue [19–21]. For example, a recent US study showed that 31% of trans individuals were unable to access hormone therapy [20]. In addition, the TGD community also struggled with general well-being and access to basic community services such as safe environments to exercise. Social factors, such as discrimination, housing, employment, and family issues, also play a large role in overall health. These issues are due to larger societal issues and policies need to be implemented to promote inclusivity, enabling safe environments for all. Financial and geographical accessibility, as well as 'gatekeeping', need to be addressed and whilst mental health support is very much desired, the cost and time required to undertake assessments and approvals for interventions were barriers. Policies need to be implemented to direct resources and adequately provide services across the country. An example would be utilising telehealth to reach those far away from metropolitan centres. Participants frequently associated lack of accessibility with poorer health outcomes, which is consistent with previous research that suggests the unique healthcare needs of TGD people, coupled with social discrimination and stigmatisation, negatively impacts their overall wellbeing significantly [19]. These findings indicate that there is a need to address issues around

transgender healthcare accessibility, such as making medical interventions more financially affordable, increasing regional access and more broadly implementing informed consent for hormone therapy.

While systematic reviews may indicate that there is a substantial amount of literature [3], TGD research has historically been problematic, with the widespread pathologisation of TGD individuals, and there are still many significant gaps in the literature. The community, overall, are supportive of research into improving TGD health outcomes and particularly desired research in hormone effects and surgical techniques. Overall, health service delivery was also a key area of research that should be implemented. Interestingly, despite much debate regarding gender as a social construct [22–24], there were views expressed that desired exploration into links between neurodevelopmental conditions and gender as well as genetic or biological indicators for validating transgender people. Research should also focus on less well-understood groups within the TGD community at large, including non-binary experiences, TGD health in aged care, and intersex conditions. There is also a need to develop ethical recommendations and guidelines in the area of transgender health research and presentation of this research, including avoiding the use of disrespectful language and intentional or unintentional misgendering of TGD individuals [25]. Research should be performed to benefit the health of communities, and addressing these broad areas of interest will ensure that research remains relevant to community needs.

There were some limitations to this study inherent in the design. Firstly, the survey was anonymous and self-reported, and data responses to these questions were not measured objectively. While some responses were detailed, many participants provided very short responses that limited inferences. There was also no control sample of non-transgender Australian individuals to use as a comparison between the healthcare experiences of transgender individuals and the wider population. There was also an over-representation of younger individuals and under-representation of older individuals, and this is likely related to online recruitment methods. Given the rapidly changing expression and understanding of gender, it is likely that the needs and wants of younger and older transgender individuals, as well as their lived experience, may be markedly different.

5. Conclusions

Findings from this large survey have highlighted a pressing need for training of health professionals in TGD cultural awareness and health needs. More gender services to meet the demand for TGD health services and in time, mainstreaming of TGD health services in primary care will likely improve accessibility to necessary health services for the TGD community. Furthermore, health service providers should also be mindful of shifting the focus when relevant to highlight the pride and positive experiences of gender diversity. Reliable health resources would complement individualised care provided by health professionals. Further research into optimal models of care and evaluation of training strategies are much needed; however, until further data is available, the community views described should be incorporated into TGD health service delivery and guide research priorities.

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RESEARCH

Cyproterone acetate or spironolactone in lowering testosterone concentrations for transgender individuals receiving oestradiol therapy

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Abstract

Background: Oestradiol with or without an anti-androgen (cyproterone acetate or spironolactone) is commonly prescribed in transfeminine individuals who have not had orchidectomy; however, there is no evidence to guide optimal treatment choice.
Objective: We aimed to compare add-on cyproterone acetate versus spironolactone in lowering endogenous testosterone concentrations in transfeminine individuals.
Design: Retrospective cross-sectional study.
Methods: We analysed 114 transfeminine individuals who had been on oestradiol therapy for >6 months in two gender clinics in Melbourne, Australia. Total testosterone concentrations were compared between three groups; oestradiol alone (n = 21), oestradiol plus cyproterone acetate (n = 21) and oestradiol plus spironolactone (n = 38). Secondary outcomes included serum oestradiol concentration, oestradiol valerate dose, blood pressure, serum potassium, urea and creatinine.
Results: Median age was 27.0 years (22.5–45.1) and median duration of hormone therapy was 1.5 years (0.9–2.6), which was not different between groups. On univariate analysis, the cyproterone group had significantly lower total testosterone concentrations (0.8 nmol/L (0.6–1.20)) compared with the spironolactone group (2.0 nmol/L (0.9–9.4), P = 0.037) and oestradiol alone group (10.5 nmol/L (4.9–17.2), P < 0.001), which remained significant (P = 0.005) after adjustments for oestradiol concentration, dose and age. Serum urea was higher in the spironolactone group compared with the cyproterone group. No differences were observed in total daily oestradiol dose, blood pressure, serum oestradiol, potassium or creatinine.
Conclusions: The cyproterone group achieved serum total testosterone concentrations in the female reference range. As spironolactone may cause feminisation without inhibition of steroidogenesis, it is unclear which anti-androgen is more effective at feminisation. Further prospective studies are required.

Key Words
- transgender persons
- transsexualism
- gender identity
- gender dysphoria
- androgens

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Introduction

Rapid rises in demand for transgender health services have been observed worldwide (1, 2). Birth-assigned males who wish to transition to female (hereafter termed transfeminine individuals) are typically treated with oestradiol as feminising gender-affirming hormone therapy (3). Goals of therapy are generally to increase serum oestradiol concentrations and lower serum total testosterone concentrations to achieve sex steroid concentrations in the female reference range. Over 3–24 months, this leads to feminine physical characteristics including softening of skin, a decrease in facial and body hair growth, changes in body fat and muscle distribution, as well as breast development (4). Oestradiol improves psychological functioning in transfeminine individuals (5); however, oestradiol alone is usually insufficient to lower serum total testosterone concentrations from a male to a female reference range. Oestradiol suppresses gonadotropin-releasing hormone (GnRH) via negative feedback, in turn partially lowering testosterone. However, as the majority of individuals (82% in our clinics (1)) do not undergo genital reassignment surgery to remove the testes, which are responsible for >95% of testosterone production, most individuals will require treatment with an additional anti-androgen drug. Anti-androgens such as cyproterone acetate or spironolactone are commonly added to oestradiol, lowering or blocking the effects of testosterone to aid development of feminising physical characteristics.

In transfeminine individuals wishing to inhibit androgenic physical characteristics, choice of anti-androgen agent is a common clinical scenario faced by patients and treating clinicians alike. Whilst both anti-androgen agents, cyproterone acetate and spironolactone, have been shown to lower serum testosterone concentrations if added to oestradiol treatment, there is little evidence to guide the superiority of one anti-androgen over another (6). Both cyproterone acetate and spironolactone have peripheral anti-androgen effects, but cyproterone acetate additionally has progestogenic actions which may be more effective in suppressing GnRH and in turn, testosterone concentrations.

As there are no data to support one drug over the other, prescription of anti-androgens is often a random choice with over 90% of experienced prescribers of gender-affirming hormone therapy using both agents with no rationale for one or the other (7). Yet, cyproterone may be associated with adverse effects such as depression, and spironolactone may be associated with excess diuresis, electrolyte imbalance and hypotension, which impact upon treatment choice.

In this retrospective audit of individuals on established feminising hormone therapy, we aimed to compare the serum total testosterone concentrations of individuals on established treatment with oestradiol alone, oestradiol with additional cyproterone acetate and oestradiol with additional spironolactone. We hypothesised that in transfeminine individuals on oestradiol therapy, a greater proportion of individuals receiving additional cyproterone acetate would have total testosterone concentrations <2 nmol/L (the female reference range in our laboratory) compared to those receiving additional spironolactone or oestradiol alone.

Methods

A retrospective audit of de-identified electronic medical records was performed of new consultations for gender dysphoria across two gender clinics in Melbourne, Australia: (a) Equinox Gender Diverse Clinic, an adult primary care general practice clinic with a focus on transgender health and (b) an adult endocrine specialist clinic. New consecutive consultations between 1 January 2011 and 31 December 2016 were analysed. As the primary care clinic commenced on 22 February 2016, data were analysed for the first 12 months of operation until 22 February 2017. The study was approved by the Austin Health Human Research Ethics Committee (LNR/17/Austin/102) and the nature of the study did not necessitate informed consent.

Clinical characteristics of the audit have been previously published (1). This cross-sectional analysis included transfeminine individuals newly presenting to the clinics who had been on established feminising hormone therapy with oestradiol for at least 6 months and had fasting serum sex steroid results available within 1 month of their initial consultation. We excluded individuals who were expected to have castrate testosterone concentrations (previous orchidectomy or concurrent GnRH agonist therapy) and individuals on ethinyl oestradiol treatment as this was not measurable on oestradiol immunoassay.

The primary outcome of interest was serum fasting total testosterone concentration by treatment group: (a) oestradiol alone, (b) oestradiol plus additional cyproterone acetate and (c) oestradiol plus additional spironolactone. Other parameters of interest included serum oestradiol concentration, potassium, urea and creatinine,

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haemoglobin, liver function (alanine transaminase (ALT)), oestradiol valerate dose and blood pressure.

As data were obtained retrospectively, sex steroid concentrations, biochemistry and haemoglobin were performed using immunoassay available as standard care for clinical decision-making. Multiple National Association of Testing Authorities (NATA, the national accreditation body for Australia) accredited laboratories available locally were used.

Statistical analyses were performed using R (v3.5.1; R foundation for statistical computing). Median (IQR) are reported and differences between were tested using Kruskal–Wallis test followed by Nemenyi *post hoc* comparisons. A linear mixed model was also fitted to compare total testosterone concentrations between the three treatment groups, adjusting for corresponding oestradiol concentrations, doses and age. Total testosterone concentrations were log-transformed to approximate normality, and results were back-transformed to show the geometric means. Differences between recruitment centres were accounted for as a random effect. *Post hoc* pairwise comparisons between the three groups with Tukey's adjustment was also performed. For all analyses, the significance level was set at 5%.

Results

Of 540 individuals in our clinical audit, 136 (36%) were birth-assigned males (transfeminine individuals). 122 were taking oestradiol but only 114 individuals had received feminising hormone therapy with oestradiol for >6 months. After excluding individuals who had previous orchidectomy ($n=28$), concurrent GnRH agonist therapy ($n=1$) and ethinyl oestradiol ($n=4$), 80 individuals had data available for analysis.

Of 80 individuals on established oestradiol therapy for >6 months, 21 were on oestradiol alone (oestradiol alone group), 21 were receiving oestradiol plus additional cyproterone acetate (cyproterone group) and 38 were receiving oestradiol plus additional spironolactone (spironolactone group).

There was no significant difference between the age and duration of hormonal therapy between the three groups. The median age was 27 years (22–45) and median duration of hormonal therapy was 1.5 years (0.9–2.6). Oral oestradiol valerate was the most common formulation used in 88.3% of individuals and the remainder used transdermal oestradiol (11.7%) which are the two most common formulations available on the Australian Pharmaceutical Benefits Scheme. The median doses used were oestradiol valerate 6 mg (4, 6), cyproterone acetate 50 mg (25, 50) and spironolactone 100 mg (87.5–200).

The serum total testosterone concentrations for the three groups are shown in Fig. 1. The median serum total testosterone concentrations were 10.5 nmol/L (4.9–17.2) in the oestradiol alone group, 0.8 nmol/L (0.6–1.2) in the cyproterone group and 2.0 nmol/L (0.9–9.4) in the spironolactone group. On univariate analysis, the cyproterone group had significantly lower serum total testosterone concentrations than the spironolactone group and the oestradiol-alone group. After adjustment for oestradiol concentration, oestradiol dose, spironolactone dose, cyproterone dose and age (Fig. 2), this remained significantly different ($P=0.005$). Findings were unchanged after excluding those on transdermal oestradiol. 90% of the cyproterone group and 40% of the spironolactone group had total testosterone concentrations <2 nmol/L.

Serum urea was higher in the spironolactone group than the cyproterone group but all results remained in the normal reference range (3–9.2 mmol/L) for the assay. No differences were observed in total daily oestradiol valerate dose, oestradiol concentration achieved, body mass index, blood pressure, haemoglobin, creatinine or ALT (Table 1).

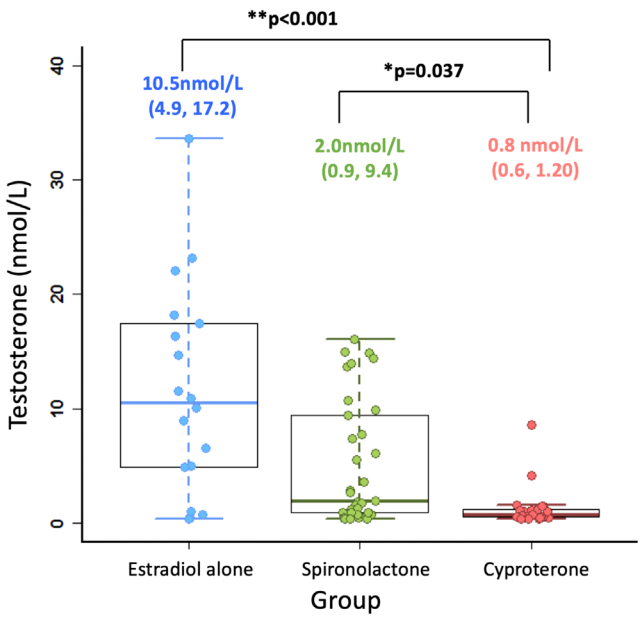

Figure 1
Box plots demonstrating median, interquartile range and range for total testosterone (nmol/L) for three groups. The median (IQR) is printed above and *P* values represent comparison with cyproterone acetate group.

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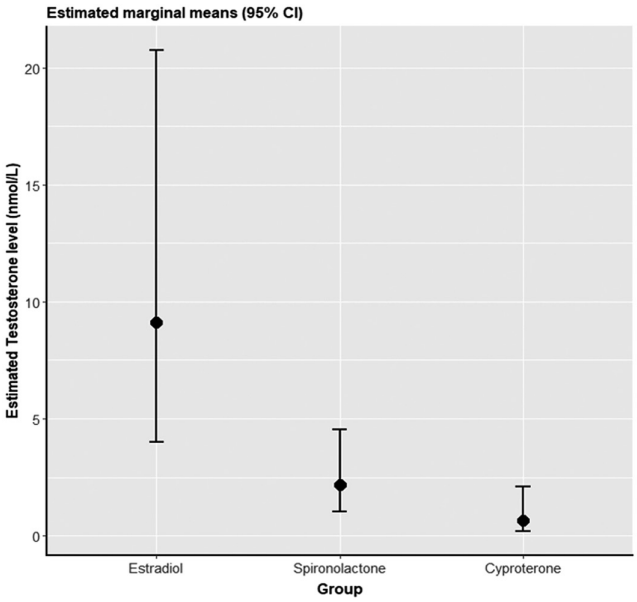

Figure 2
Estimated marginal means (95% CI) for the three groups from a linear mixed model adjusting for oestradiol concentration, oestradiol dose, spironolactone dose, cyproterone dose and age, with recruitment centre as random effect. Total testosterone concentrations were back-transformed to show the geometric mean of each group.

Discussion

In this retrospective cross-sectional analysis, transfeminine individuals undergoing feminising hormone therapy with oestradiol achieved the lowest total testosterone concentrations with additional cyproterone acetate when compared to additional spironolactone or oestradiol alone. Serum urea concentrations were higher in the spironolactone group than the cyproterone group and oestradiol alone group but no differences were observed in serum creatinine. No differences were observed in the serum oestradiol concentration achieved, total oestradiol valerate dose required, blood pressure or liver function between the three groups.

Supporting our findings, a recently published US retrospective audit of 98 transfeminine individuals found only a quarter of those on spironolactone achieved total testosterone concentrations in the female reference range (8). Notably, although cyproterone has been used internationally for many years, it is not available in the US due to rare case reports of hepatotoxicity in men receiving high doses for prostate cancer (9). Reasons for the variable effects of spironolactone and cyproterone on serum testosterone concentrations may well be related to differing mechanisms of action.

Spironolactone is a mineralocorticoid receptor antagonist and is anti-androgenic in four ways. First, it is a peripheral androgen receptor partial antagonist (IC50 = 77 nmol/L) (10). The IC50, which is the concentration of an inhibitor where the binding is reduced by half, is higher than that of cyproterone acetate, reflecting less potency. Second, spironolactone is a weak inhibitor of 17α-hydroxylase and 17,20-lyase (enzymes in the testosterone biosynthetic pathway) which lowers testosterone to a small degree. Third, it has weak progestogenic activity with a very low half-maximal potency (10); and fourth, it has oestrogenic activity expected to suppress GnRH and gonadotropins at the hypothalamus and pituitary (10). However, even at high doses, small pharmacokinetic studies in healthy males show no significant reduction in serum testosterone, despite a transient rise in FSH and LH in the first 2 days of administration (11, 12). Interestingly, administration of the main metabolite of spironolactone, canrenone, appears to decrease testosterone by 50–60% within hours in healthy men (13) and in conjunction with oestradiol, spironolactone decreases testosterone (14).

Table 1 Comparison of secondary outcomes by treatment group.

Parameter	Group *n* = 80 (total)			*P* value
	Oestradiol alone (*N* = 21)	Cyproterone (*N* = 21)	Spironolactone (*N* = 38)	
Urea (mmol/L)	4.9 (4.2–5.8)	4.2 (3.6–5.1)	5.0 (4.3–6.0)	0.035
Creatinine (μmol/L)	78 (72–96)	72 (63–75)	77 (69–85)	0.069
Oestradiol valerate dose (mg)	6 (4–6)	5 (4–6)	6 (4–6)	0.601
Oestradiol concentration (pmol/L)	256 (119–408)	279 (149–334)	279 (233–384)	0.795
BMI (kg/m^2)	27.2 (23.1–31.9)	24.5 (23.4–30.3)	24.7 (23.5–31.0)	0.989
Systolic BP (mmHg)	125 (121–131)	123 (118–136)	125 (120–136)	0.941
Diastolic BP (mmHg)	80 (75–81)	85 (80–90)	80 (75–82)	0.056
Haemoglobin (g/L)	147 (143–159)	148 (143–151)	146 (138–158)	0.880
ALT (U/L)	21 (15–28)	23 (15–29)	19 (14–24)	0.630

Median (IQR) are presented. *P* values refer to overall difference between the groups and are obtained from the Kruskal–Wallis test as a non-parametric alternative to *t*-test.

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Cyproterone acetate is a steroidal anti-androgen and works in two ways. First, it is a potent peripheral androgen receptor competitive antagonist (IC50 = 7.1 nmol/L) acting at peripheral sites (i.e. skin, hair, body fat, muscle) to decrease the effect of testosterone (15). Second, it activates the progesterone receptor which, similar to oestradiol treatment, causes further negative feedback to suppress GnRH and gonadotropins at the hypothalamus and pituitary respectively to lower testosterone production (16, 17). As spironolactone may potentially cause feminisation by direct antagonism of the androgen receptor without reduction of serum testosterone, it is unclear which anti-androgen is more effective at feminisation and prospective studies are required.

Serum urea was noted to be higher in the spironolactone group compared to the cyproterone group and oestradiol alone group. This is likely related to the diuretic effect of spironolactone, however reassuringly despite a reasonably high median dose of spironolactone (100 mg daily), serum urea in the spironolactone group remained within normal reference range and no changes between groups were observed in haemoglobin, serum creatinine or blood pressure.

Serum oestradiol concentrations achieved were no different between the groups and were generally between 250 and 350 pmol/L on a relatively high median dose of oral oestradiol valerate of 6 mg daily. This dose is certainly higher than that used in the European Network for Investigation of Gender Incongruence (4 mg) (18), yet oestradiol concentrations achieved are lower than the recommended concentrations (367–734 pmol/L) in international guidelines (3). Notably, no studies have examined what oestradiol concentrations are optimal in transfeminine individuals and guideline recommendations are based on predominantly expert opinion. Moreover, there are no prospective studies examining the effectiveness of different formulations and doses of oestradiol therapy for feminisation. Further research is required to optimally guide clinical care.

There are a number of limitations to this retrospective cross-sectional analysis inherent in the design and small numbers of individuals. Individuals were not randomised to the groups which may confound results and we did not have details regarding rationale for choice of anti-androgen drug. Importantly, we cannot account for factors such as clinician preference or whether patients taking oestradiol alone or spironolactone may have accepted or desired higher testosterone levels. We also did not have data regarding feminising physical characteristics and due to differing mechanisms of action of cyproterone acetate and spironolactone, serum total testosterone concentrations alone may not necessarily represent effectiveness of feminisation. Due to the cross-sectional nature of the study, adverse effects of medications were not able to be determined. Total serum testosterone concentrations were measured by immunoassay, which lacks precision at low serum testosterone concentrations (as opposed to more sensitive liquid chromatography-tandem mass spectrometry (LC-MS)), as sex steroid concentrations were performed as part of standard care for clinical decision-making. As a result, sex steroid concentrations were performed at various NATA-accredited laboratories. Nonetheless, this is the first comparison of the effect of cyproterone acetate and spironolactone on total testosterone concentrations and given the lack of research in the transgender field, our findings may have implications for clinical decision-making for transfeminine individuals who have not undergone orchidectomy.

Conclusions

As gender-affirming hormone therapy is typically given lifelong and commenced at a young age, selecting the optimal anti-androgen to suppress serum testosterone and hence aid feminisation is a highly important decision for patients and clinicians alike. Cyproterone is highly effective at lowering endogenous total testosterone concentrations in transfeminine individuals undergoing feminising hormone therapy. Due to differing mechanisms of action, differences in anti-androgenic or feminising effects of cyproterone and spironolactone are unclear. Further prospective research studies are required.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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ORIGINAL ARTICLES

Cross-sex hormone therapy in Australia: the prescription patterns of clinicians experienced in adult transgender healthcare

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Key words
transgender persons, gender dysphoria, estradiol, testosterone, clinical decision-making.

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Abstract

Background: Despite increasing demand for transgender healthcare, guidelines for cross-sex hormone therapy are based on low-level evidence only. As most data are based on international expert opinions, interpretations and practices vary significantly.
Aims: To aid the development of Australian clinical guidelines, we aimed to identify cross-sex hormone therapy prescribing patterns among medical practitioners experienced in adult transgender healthcare.
Methods: We conducted an anonymous online survey of experienced hormone prescribers who were members of the Australian and New Zealand Professional Association for Transgender Health (ANZPATH).
Results: We received 35 responses from 43 individuals listed with ANZPATH. Mental health assessments prior to commencement of hormonal therapy were recommended by 80% of prescribers. The preferred first-line masculinising hormone therapy was intramuscular testosterone undecanoate (46% of respondents). The most commonly prescribed feminising agents were oral estradiol valerate (first line in 71.4%), with either spironolactone or cyproterone acetate. Most respondents (>90%) targeted sex steroid reference ranges of the affirmed gender, and 71.4% reviewed individuals every 2–3 months in the first year. Better training for doctors was seen as the most pressing priority for government funding, and 79.3% supported the development of local Australian-based guidelines.
Conclusions: Experienced hormone prescribers in Australia largely use medication regimens and monitor sex steroid levels and potential adverse effects of sex hormone therapy in accordance with broad, subjective recommendations listed in international guidelines. Additional practitioner training is necessary, and local Australian-based guidelines would offer specific, relevant guidance to clinicians in the initiation and monitoring of cross-sex hormone therapy for adult transgender individuals.

Introduction

Cross-sex hormone therapies (otherwise known as hormone therapies or gender-affirming hormone therapies) are often prescribed to alleviate gender dysphoria – the distress many transgender individuals experience when their gender identity is markedly and persistently incongruent from their birth-assigned sex. Aligning a person's physical characteristics with his/her gender identity may involve non-medical interventions such as binders and protheses, as well as medical interventions such as masculinising or feminising hormone therapies and surgical interventions. The prescription and monitoring of hormone regimens, which may include testosterone or estradiol replacement as well as anti-androgen agents, are the focus of this study.

The consequences of delaying access to hormone therapies are significant. Australian studies demonstrate that over 70% of transgender people have medically diagnosed depression, and 48% have attempted suicide, numbers far higher than population prevalence rates,

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noting the potential for responder bias.[1–3] Despite consensus between clinicians and individuals whose lived experience confirms the critical and often life-saving role of hormone treatment, research in the transgender field is in its infancy. Sound evidence suggests that hormonal treatment in transgender individuals decreases the risk of suicide,[4,5] alleviates gender dysphoria and improves psychological functioning and overall quality of life.[6,7]

Although the World Professional Association for Transgender Health[8] and the US Endocrine Society[9] have published international guidelines on various regimens for hormonal treatment of transgender individuals, the evidence on which the recommendations are based is low-level – often citing expert opinion rather than clinical evidence. Randomised controlled trials to guide clinical choice and monitoring of hormonal therapy do not yet exist. Recommendations are therefore broad and open to interpretation. In addition, there are differences internationally with availability, access and cost of various medications, which significantly influence prescribing patterns. The Australian and New Zealand Professional Association of Transgender Health (ANZPATH) promotes communication and collaboration among professionals involved in the healthcare of transgender individuals. ANZPATH membership signifies a level of interest and involvement in transgender healthcare above that of a regular healthcare practitioner. Among the ANZPATH electronic mailing list discussion groups, we observed wide-ranging approaches and prescribing practices, reflecting the limitations of the currently available guidelines. Although prescribers may technically be working within the current guidelines, patients seeing more than one prescriber or health service may be exposed to differing or inconsistent advice. Developing guidelines relevant to the Australian context would therefore be beneficial but first requires an understanding of current local practices.

The aim of our study was to determine hormone therapy-prescribing patterns among medical practitioners experienced in providing adult transgender healthcare in Australia. Given the lack of evidence in the field, this would enable the development of a local consensus to inform Australian clinical guidelines for the management of transgender individuals. We hypothesised that, due to the ambiguity of current international guidelines, opinion regarding choice of first-line hormonal therapy would vary significantly.

Methods

This anonymous survey of hormone therapy-prescribing patterns for adult transgender individuals was open to registered medical practitioners who were members of ANZPATH from 30 September to 31 October 2017. The survey was advertised at the ANZPATH Biennial Meeting in Sydney, Australia, on 1 October 2017. In addition, the 43 hormone prescribers (general practitioners, endocrinologists, sexual health physicians and gynaecologists) – members of ANZPATH and listed as service providers in Australia (or known to be hormone prescribers) – were invited to participate through direct email in October 2017. Participants were invited to complete the survey to assess cross-sex hormone therapy-prescribing patterns in adult transgender individuals through a link to an online survey platform provider (SurveyMonkey). The study was approved by the Austin Health Human Research Ethics Committee (HREC/17/Austin/372).

Inclusion criteria assessed by two screening questions were: (i) registered medical practitioners in Australia or New Zealand; and (ii) prescribers of hormonal therapy to transgender individuals.

Demographics

Demographic data were obtained from respondents, including gender, age range, state or territory of practice, postcode of practice, type of healthcare provider (general practice, psychiatry, sexual health, endocrinology, gynaecology, paediatrics, surgical or other), case load (number of transgender patients treated per month), experience (number of years treating transgender individuals) and participation in teaching transgender medicine.

Informed consent model

Questions were designed to gauge perspectives on the requirement for a formal mental health assessment prior to the commencement of hormonal therapy – at times described as a potential barrier to healthcare.[1] Current standards of care place a strong emphasis on involving a mental health professional to diagnose gender dysphoria and assess criteria for hormone therapy.[8,9] An informed consent model is an alternative approach.[10] While informed consent is integral before the commencement of any treatment, the informed consent model is defined as a model of care in which, following appropriate education, a decision for hormone treatment is shared by the patient and a trained clinician (without a formal mental health assessment).

Cross-sex hormone therapy-prescribing patterns

In addition, questions were designed to assess prescribing patterns and clinical treatment practices, including the

following: advice regarding fertility, reference to clinical practice guidelines, preferred testosterone and oestrogen preparations, use of anti-androgen and progesterone treatments, frequency of monitoring after commencement of hormonal therapy, investigations used during monitoring and treatment targets.

Practitioners were also asked for their views on priority areas for government funding and their perspectives on the need for Australian-based clinical guidelines. The survey preamble and questions in full are included in Supporting Information Appendix SI.

Statistical analysis was performed using SPSS Statistics version 23 (IBM Corporation, NY, USA).

Results

Of the 43 invitations to participate in the study sent to medical practitioners experienced in providing transgender healthcare, 35 responses were received. Demographic characteristics of the respondents are shown in Table 1.

Informed consent model

When asked whether the practitioner recommended a mental health assessment by a psychologist or psychiatrist before starting hormone treatment, 80% of practitioners responded 'yes, always' or 'yes, usually', and 20% responded 'sometimes'. However, when asked whether practitioners followed an informed consent model, 48% responded 'no, never', 26% responded 'sometimes', 20% responded 'yes, usually' and 6% responded 'yes, always'. All practitioners (100%) provided advice regarding fertility implications prior to starting hormone therapy.

Cross-sex hormone therapy-prescribing patterns

Masculinising hormone therapy

Intramuscular testosterone undecanoate was the preferred first-line option for over 50% of practitioners prescribing masculinising hormone therapy (Table 2). Almost all practitioners (97%) targeted treatment to achieve total testosterone levels within the typical male reference range (total testosterone 10–30 nmol/L), and 3% targeted treatment to free testosterone 300–500 pmol/L rather than total testosterone levels. Investigations monitored regularly included total testosterone levels (76% of respondents monitored this at most visits), estradiol levels (61%), full blood examination, electrolytes and renal function (61%) and liver function tests (73%). Occasional investigations (e.g. annually) included calcium, vitamin D, cancer screening, glucose and lipid profile. Mixed responses

Table 1 Participant characteristics of 35 respondents

Characteristic	*n* (%)
Gender	
Female	19 (54.3)
Male	14 (40.0)
Trans and gender diverse†	2 (5.7)
Age (years)	
20–29	1 (2.9)
30–39	8 (22.9)
40–49	12 (34.3)
50–59	10 (28.6)
60–69	3 (8.6)
>70	0 (0)
No response	1 (2.9)
State or territory	
Victoria	20 (57.1)
Queensland	5 (14.3)
Western Australia	4 (11.4)
New South Wales	3 (8.6)
Australian Capital Territory	1 (2.9)
Tasmania	1 (2.9)
South Australia	0 (0)
Northern Territory	0 (0)
No response	1 (2.9)
Practice location	
Metropolitan	31 (88.6)
Rural/remote	3 (8.6)
No response	1 (2.9)
Sub-specialty	
General practice	22 (62.9)
Endocrinology	7 (20.0)
Sexual health	6 (17.1)
Type of practice	
Private clinic	28 (80.0)
Public hospital-based gender clinic	3 (8.6)
Public sexual health clinic	3 (8.6)
No response	1 (2.9)
Number of years treating transgender individuals	
<5	13 (37.1)
6–10	12 (34.3)
11–20	4 (11.4)
>20	6 (17.1)
Average number of transgender patients seen per month	
<5	7 (20.0)
6–10	9 (25.7)
11–20	8 (22.9)
>20	11 (31.4)
Involvement in teaching or training in transgender medicine	
Yes	19 (54.3)
No	13 (37.1)
No response	3 (8.6)

†As not all individuals with non-binary gender identities identify with the term transgender, the term trans and gender diverse was used in the survey as an inclusive umbrella term to describe all those whose gender identity is incongruent with their birth-assigned sex.

were received regarding bone mineral density, with monitoring occurring 'occasionally' in 33%, 'once-off' in 30%, and 'never' in 36%. Despite regular test monitoring, the majority of practitioners (52%) did not target serum estradiol levels in individuals receiving testosterone therapy.

Feminising hormone therapy

Oral estradiol valerate was the most preferred first-line treatment option for most practitioners (Table 2). In addition to estradiol, anti-androgen treatments were 'often' or 'almost always' used by 90% of practitioners, and both spironolactone and cyproterone acetate were frequently prescribed (Table 2). Progesterone for the purpose of breast development was infrequently prescribed: of the 29 respondents, 48.3% prescribed it 'sometimes', 44.8% 'never' and the remaining 6.9% 'other'.

Table 2 Preferred cross-sex hormone therapy medications (*N* = 35)

	n (%)
Preferred first-line masculinising testosterone preparations	
Testosterone undecanoate (intramuscular)	17 (48.6)
Testosterone enantate (intramuscular)†	11 (31.4)
Testosterone gel/cream	5 (14.3)
Transdermal testosterone patch	0 (0)
Oral testosterone undecanoate	0 (0)
Other	0 (0)
No response	2 (5.7)
Preferred first-line feminising estradiol preparations	
Estradiol valerate (oral)	25 (71.4)
Oral combined contraceptive pill containing ethinyl estradiol	0 (0)
Transdermal estradiol patch	3 (8.6)
Oestrogen implants	0 (0)
Estradiol intramuscular injections	0 (0)
Other‡	1 (2.9)
No response	6 (17.1)
Do you use anti-androgen treatments in addition to estradiol therapy?	
Almost always	20 (57.1)
Often	6 (17.1)
Sometimes	2 (5.7)
Only if I can't suppress the testosterone on estradiol alone	1 (2.9)
No response	6 (17.1)
Anti-androgen medications used (more than one option could be selected)	
Spironolactone	27 (93.1)
Cyproterone acetate	28 (96.6)
5-alpha reductase inhibitors (finasteride, dutasteride)	10 (34.5)
Bicalutamide	1 (3.5)
No response	6 (17.1)
Do you prescribe progesterone for breast development?	
Almost always	0
Often	0
Sometimes	14 (40.0)
Never	13 (37.1)
Other	2 (5.7)
No response	6 (17.1)

†At the time of the survey, testosterone enantate was still available on the PBS; however, this was removed from the PBS in February 2018.
‡Other response was 'depends on age of patient; transdermal in older, oral in younger'.

The majority of practitioners (93%) targeted serum estradiol in the female reference range of approximately 200–799 pmol/L, with 3.5% aiming for higher levels at 700–1199 pmol/L and 3.5% assessing feminisation clinically, without measuring levels. Total testosterone targets used were in the female reference range <2 nmol/L in 59% of practitioners, between 2 and 5 nmol/L in 14%, between 6 nmol/L and the lower limit of the male reference range in 7%, assessed clinically without measuring levels in 10% and 'other' in 10%.

For individuals receiving feminising hormone therapy, investigations monitored regularly at most visits included total testosterone levels (83% of respondents), estradiol levels (86%), full blood examination (66%), electrolytes and renal function (69%) and liver function (69%). Occasional investigations (e.g. annually) included calcium, vitamin D, cancer screening, glucose and lipid profile. Similar to those on testosterone therapy, mixed responses were received regarding bone mineral density.

Monitoring

Most practitioners reviewed patients during the first year of hormone therapy every 2–3 months (71.4%) or every 4–6 months (17.1%).

Funding priorities and guidelines

When asked to select their top priority for government funding, 44.8% of respondents answered 'better training for doctors in trans issues', 24.1% selected 'gender clinics', 17.2% selected 'psychology/psychiatry services' and 10.3% selected 'medical research'. The majority (79.3%) of practitioners supported the need for Australian-based clinical guidelines for the treatment of transgender individuals.

Discussion

Among a cohort of Australian medical practitioners experienced in prescribing hormone therapy, we found that the most preferred forms of masculinising and feminising hormones were, respectively, intramuscular testosterone undecanoate and oral estradiol valerate. Anti-androgen therapy with either spironolactone or cyproterone acetate was frequently prescribed. Australian prescribing patterns are influenced by availability,

Pharmaceutical Benefits Scheme (PBS) access and cost. Since this survey concluded, there has been discontinuation of a transdermal testosterone solution formulation (Axiron) and the withdrawal from PBS of testosterone enantate (Primoteston), which will undoubtedly have an effect on future prescribing. Interestingly, cyproterone acetate is the anti-androgen agent used almost exclusively in Europe, whereas it has never been approved by the Food and Drug Administration in the United States, and therefore, Australia is in a unique position to have similar access to both agents. GnRH analogues are not PBS listed for transgender adults in Australia and are therefore rarely used due to prohibitively high costs.

Most cross-sex hormone therapy was delivered in primary care, in private clinics, which may well reflect a lack of public gender services around Australia and insufficient training of endocrinologists and sexual health physicians. The large majority of prescribers treated to achieve testosterone and estradiol levels in the reference range of the affirmed gender and regularly monitored sex steroid levels, liver function tests, electrolytes and full blood count every 2–3 months in the first year of treatment.

Opinions regarding the use of an informed consent model of care were varying; however, in almost all situations, mental health assessment and support prior to commencement of hormone treatment was recommended by prescribers. Notably, practice is likely dependent on individual patient interactions and may well have been difficult to quantitate in a survey. In addition, the recently released World Health Organisation's International Classification of Diseases 11th Revision (ICD-11) no longer classifies gender incongruence as a mental health disorder, which will influence the future provision of healthcare. As increasing numbers of physicians gain experience in treating transgender individuals, it is likely that there will be a move away from the standard approach to an informed consent model, which must still include mental health support. With an informed consent model, mental health practitioners remain an important part of the multidisciplinary team to manage mental health comorbidities and provide support during social and medical gender transition if required. Any holistic plan for care encompassing adequate mental health support (provided by GP or mental health professionals) must be individualised, affirming and respectful of the patient.

Prescribing patterns observed are generally in keeping with recommendations of international guidelines.[8,9] With masculinising hormone therapy for transgender males, testosterone mono-therapy is effective at inducing masculinisation; however, there have been no randomised controlled trials to guide the optimal route or the optimal dose of therapy. Prescribers regularly monitor potential adverse effects of polycythaemia[11] and liver abnormalities,[12] which are recommended in the product information for transdermal testosterone and testosterone undecanoate. Given the role of testosterone and estradiol in modulating lipid levels[13] and insulin resistance,[14] and the fact that increased mortality in transgender individuals appears to be related to cardiovascular disease,[15,16] it is reasonable that cardiovascular risk factors are monitored periodically. Low estradiol levels often occur, particularly in trans male (female-to-male) individuals whose ovaries have been removed, potentially leading to adverse bone and metabolic effects. A recent animal model of cross-sex hormone therapy in female-to-male individuals suggests that the addition of low-dose estradiol to testosterone therapy in ovariectomised mice can improve atherosclerotic plaque[17] and preserve bone architecture;[18] however, this requires further study in humans.

No clear consensus emerged on the monitoring of bone mineral density, and there are insufficient data to suggest that testosterone therapy or estradiol therapy in transgender adults causes adverse effects on bone density[19]. Current international guidelines recommend that clinicians obtain bone mineral density measurements only when risk factors for osteoporosis exist, specifically in those who cease sex hormone therapy after gonadectomy.[9]

Feminising hormone therapy is more complex as estradiol alone is usually insufficient to lower endogenous testosterone levels to the female reference range, and anti-androgens are almost always required (typically cyproterone acetate or spironolactone). As transdermal estradiol avoids the first pass liver effect, there is a theoretical benefit of decreased arterial and venous thromboembolism. However, there have been no prospective, randomised controlled trials evaluating oral versus transdermal estradiol in any population (transgender or postmenopausal women), and any observational case–control studies have been conducted on relatively high-risk populations in postmenopausal women.[20,21] One large population-based study of postmenopausal women has shown a similar increased risk of stroke when comparing oral estradiol and high-dose (>50 mcg/day) transdermal estradiol – those typically used in trans females;[22] however, in contrast, meta-analyses suggest that transdermal oestrogens carry minimal or no thrombotic risk,[23] with minimal effects on haemostatic variables.[24] Without data for the transgender population specifically, we must extrapolate based on studies of postmenopausal women. These suggest that, while absolute risks of thromboembolism are low, there does appear to be a dose–response relationship and a higher probability in

those with cardiovascular risk factors.[25] As such, the lowest dose necessary to induce feminisation should be used, and transdermal routes may be more appropriate for those at high risk of thromboembolism; however, the data to support this are scant. From a practical perspective, the preference for oral routes as first-line treatment may reflect the fact that adherence of the patch is an issue, particularly if there is excessive hair or sweat on the skin.

Monitoring practices for individuals on feminising hormone therapy is similar to those on masculinising hormone therapy; however, in addition, those receiving spironolactone should have their electrolytes and renal function measured periodically.[9]

Providers considered education of health professionals to be a priority for government funding, and careful consideration should be given to evaluating the best methods of delivering such education, not only at undergraduate and postgraduate levels but also to clinicians. Given the increasing visibility of transgender individuals and rising demand for transgender health services seen worldwide, it is likely that all clinicians will need awareness of gender-affirming care. Although Australian data are lacking, only 30% of North American medical schools had provided any training relating to transgender healthcare.[26] Participants in our survey expressed widespread support for the development of Australian clinical guidelines on the treatment of transgender individuals, and this may well be an effective means of educating and supporting health professionals in prescribing hormone therapy.

There were several key limitations to this survey. The study was small; however, practitioners experienced in transgender healthcare are few in Australia, and we had a high response rate – likely capturing a representative sample of clinicians of varying ages and clinical experience. We advertised the study to ANZPATH members only and, as such, may not have captured all relevant hormone prescribers in Australia. However, this was so that only those with a certain level of interest and involvement in transgender healthcare would be surveyed. Responder bias may have impacted results. There was a predominance of Victorian respondents that may have skewed practices; however, a previous Australian transgender community survey has similarly demonstrated that the greatest number of respondents reside in Victoria.[2] No responses were received from South Australian, Northern Territory or New Zealand prescribers.

Conclusion

A greater evidence base is required to guide best treatment and clinical care practices in transgender health, particularly as the majority of individuals will require treatment lifelong. Realistically, it will be many years before such evidence is available, and until then, clinical decisions will be based on expert opinion only. Experienced hormone prescribers in Australia largely use medication regimens and monitor sex steroid levels and potential adverse effects of sex hormone therapy in accordance with broad recommendations listed in international guidelines. Further education on transgender healthcare is needed. The development of guidelines adapted for the Australian context would be a valuable resource for clinicians initiating and monitoring hormone therapy in adult transgender individuals. This study provides the first insight into the current Australian hormone prescribing practices among experienced medical practitioners in adult transgender medicine.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Preamble and survey questions.

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Sociodemographic and Clinical Characteristics of Transgender Adults in Australia

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Abstract

Background: Over the last 10 years, increases in demand for transgender health care has occurred worldwide. There are few data on clinical characteristics of Australian adult transgender individuals. Understanding gender identity patterns, sociodemographic characteristics, gender-affirming treatments, as well as medical and psychiatric morbidities, including neurobehavioral conditions affecting transgender and gender-diverse adults will help to inform optimal health service provision.

Purpose: In an Australian adult transgender cohort, we aimed to first, assess referral numbers and describe the sociodemographic and clinical characteristics, and second, to specifically assess the prevalence of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).

Methods: We performed a retrospective audit of deidentified electronic medical records in a primary care and a secondary care gender clinic in Melbourne, Australia. Annual referral rates, sociodemographic data, and prevalence of medical and psychiatric conditions were obtained.

Results: Data for 540 transgender individuals were available. Rapid rises were observed in referrals for transgender health services, more than 10 times the number in 2016 compared with 2011. Median age at initial presentation was 27 years (interquartile range (22, 36), range 16–74). Around 21.3% were unemployed and 23.8% had experienced homelessness despite high levels of education. Around 44.1% identified as trans male, 36.3% as trans female, and 18.3% as gender nonbinary. Medical morbidities were rare but mental illness was very common. The prevalence of depression was 55.7%, anxiety in 40.4%, ADHD in 4.3%, and ASD in 4.8%, all higher than reported age-matched general Australian population prevalence.

Conclusions: Rising demand for transgender care, socioeconomic disadvantage, and high burden of mental health conditions warrants a comprehensive multidisciplinary approach to provide optimal care for transgender individuals. Given that ASD and ADHD are prevalent, in addition to gender-affirming treatments, psychosocial interventions may assist individuals in navigating health care needs and to support social aspects of gender transition. Further studies are required to understand links between ASD, ADHD, and gender identity and to evaluate optimal models of health service provision for transgender individuals.

Keywords: attention deficit disorder with hyperactivity; autistic disorder; depression. gender dysphoria; transgender persons

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Introduction

There is increasing recognition of the need for adequate health services to meet the needs of transgender individuals. Transgender people, whose gender identity is markedly and persistently incongruent with their biological sex, almost always experience gender dysphoria. Characterized by severe distress and discomfort, gender dysphoria compels transgender individuals to seek treatment. In addition to gender transition, complexities such as high rates of depression and potentially neurobehavioral conditions, such as autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) may require specific treatment and affect transition-related care.[1] Addressing the specific health needs of individuals with gender dysphoria are required to optimize quality of life and social functioning.

Despite reported increases in demand for adult and pediatric transgender health services in recent years,[2–4] there are few data on clinical characteristics of Australian adult transgender individuals. Gender-affirming interventions, including hormonal and surgical interventions are not well profiled.[5] Increased understanding of gender identity patterns, sociodemographic and clinical characteristics of transgender, and gender diverse adults, including psychiatric and medical burden will help to inform health service provision.

Mental health conditions have been reported to have higher prevalence within transgender populations and there have been many reports of high rates of depression and anxiety[6–8] occurring in transgender adults. There also has been a suggestion that personality disorders[9,10] and eating disorders[11] may be more prevalent among transgender individuals. Co-occurrence with ASD has been described in children and adolescents,[12,13] and while much of the literature has associated autism traits detected on screening tests with gender dysphoria,[14,15] only one study has assessed prevalence of the diagnosis of ASD among adult transgender individuals.[16] However, not all studies have reported a higher prevalence of ASD in transgender individuals,[17,18] suggesting that high scores on autism screening tests may be potentially related to high social anxiety. A potential higher prevalence of ADHD among 54 transgender individuals in an online survey has also recently been reported.[19] Further study is warranted given that neurobehavioral conditions may affect assessment of gender dysphoria, require specific treatment, and affect the delivery of individualized supportive care.

Hormonal therapy for gender transition involves the administration of testosterone for masculinization, or estradiol for feminization. As testosterone and estradiol play important roles in cardiovascular disease,[20] there is also uncertainty regarding cardiovascular risk among transgender individuals.[21] Increased cardiovascular morbidity and mortality has been observed in retrospective clinical studies.[22,23] This is plausible given that hormonal therapy with testosterone and estradiol both appear to be associated with lipid derangements and potentially worsening cardiovascular risk factors such as hypertension and insulin resistance.[24,25] Further study is required.

We hypothesized first that there would be a rising number of transgender individuals seeking adult health services in Australia. Second, we hypothesized that gender identity distribution and demographic data would be different in endocrine specialist clinics compared with primary care. Specifically, as current Australian Pharmaceutical Benefits Scheme subsidy for testosterone therapy requires specialist assessment, we hypothesized that greater proportion of transgender males seeking testosterone therapy would be seen in the specialist setting. Third, given recent reports,[16,19] we hypothesized that ADHD and ASD would be more prevalent among transgender adults attending gender clinics than those in the general population.

The aims of this descriptive study in adult transgender individuals were first, to document the number of new transgender individuals seeking health care; second, to describe the gender identity patterns, sociodemographic and clinical characteristics, including gender-affirming treatments of transgender individuals in Australia; and third, we aimed to specifically assess the prevalence of ADHD and ASD among this cohort of adult transgender individuals.

Methods

A retrospective audit of electronic medical records was performed of new consultations for gender dysphoria at a primary care general practice clinic and an endocrine specialist clinic in Melbourne, Victoria, Australia. Individuals with gender dysphoria attending endocrine specialist clinics were compared those attending a primary care gender clinic, Equinox Gender Diverse Health Center operated by Thorne Harbour Health to obtain a more representative sample of transgender individuals in the community. In Australia, primary care general practitioners are the first point of medical care and play a central role in delivery of health care. A referral is required from a general practitioner to see an endocrine specialist. New consecutive consultations

between 1st January 2011 and 31st December 2016 were analyzed. As the primary care clinic only commenced on 22nd February 2016, data were analyzed for the first 12 months of operation until 22nd February 2017. The study was approved by the Austin Health Human Research Ethics Committee (LNR/17/Austin/102) and the nature of the study did not require informed consent.

New presentations to both clinics (at initial consultation) were recorded in a deidentified manner. Self-reported gender identity as recorded on registration forms were classified into four groups: trans female (birth-assigned males who identified as female), trans male (birth-assigned females who identified as male), nonbinary (those that identified as neither male nor female), and unassigned (where individuals were undecided regarding their identity).

Sociodemographic parameters included age at presentation, residential postcode (classified using the Australian Standard Geographical Classification Remoteness Area (ASGC-RA) score), educational level, employment status, smoking status (nonsmoker, current smoker), hazardous alcohol intake (defined as >2 standard drinks per day on a regular basis or binge drinking), and history of homelessness was defined as those without a permanent residential address based on the Australian Bureau of Statistics official definition (lack of an adequate dwelling, lack of tenure or if living arrangements did not allow control of, or access to space for social relations).

Clinical characteristics recorded included medical morbidities and psychiatric conditions listed as diagnoses in the medical record by clinicians. Charlson Medical Comorbidity Index was calculated as a quantitative measure of overall medical morbidity.[26] The Charlson Medical Comorbidity Index predicts mortality in individuals with multiple morbidities, such as heart disease, AIDS, or diabetes (a total of 22 conditions contribute to the score and low scores reflect low morbidity). A history of gender-affirming surgery and the gender-affirming hormone therapy regimens used were also recorded. To provide an additional assessment of cardiovascular risk, systolic and diastolic blood pressure (mmHg), height (cm), weight (kg), and body mass index (kg/m^2, BMI) at initial consultation were also collected.

Statistical analysis

Clinical characteristics are reported as median and interquartile range [median (IQR)] or number and proportion [*n* (%)] where appropriate. Statistical tests were performed as an exploratory analysis. Differences in sociodemographic and clinical characteristics between the two clinics were examined using Fisher's exact test and Student's *t*-test, or Mann–Whitney U test as its nonparametric alternative, as appropriate. A proportions test by *p*-value was performed to investigate differences in percentage of psychiatric conditions between the two clinics. The number of new consultations per year from the endocrine specialist clinic during 2011 to 2016 was also reported with a test for nonlinear trend. Statistical analysis was performed using R statistical software version 3.4.0. $p<0.05$ was considered statistically significant.

Results

Data were collected on a total of 540 new consultations; 283 from an adult endocrine specialist clinic and 257 from a primary care clinic. We observed a 10-fold increase in the number of transgender individuals newly attending endocrine specialist

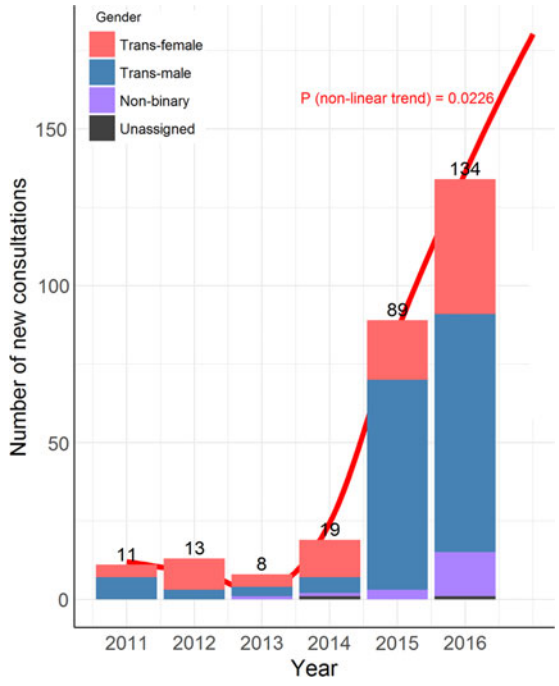

FIG. 1. New consultations at endocrine specialist clinic. Number indicates the total number of new consultations during each year from January to December. Global test for nonlinear trend from inclusion of a second-degree polynomial term in Poisson regression (df = 1; *F*-value = 18.83; $p = 0.022$).

clinics between 2011 and 2016 (Fig. 1–Global test for nonlinear trend from inclusion of a second-degree polynomial term in Poisson regression (df = 1; *F*-value = 18.83; $p = 0.022$)). Annualized data were not available for primary care.

Sociodemographic characteristics

Gender identity. The gender identities of transgender individuals attending both practices are listed in Table 1. Significantly greater proportions of trans male individuals were seen in the endocrine specialist clinic compared with primary care ($p < 0.001$ following pairwise tests with Bonferroni correction). Individuals identifying as gender nonbinary in primary care comprised 30.4% of all transgender individuals, and 7.4% in specialist clinics.

Age and location of residence. Median age was 27 years (22, 36) with range 16–72 years. Telehealth consultations were frequently performed in endocrine specialist clinics with 31% of the 283 referred individuals residing in regional or remote areas of Australia (ASGC 1–5). Homelessness had been experienced by 23.8% of the total cohort.

Education and employment. Level of education was higher than age-matched Australian population mean with a formal nonschool qualification above secondary level attained in 73.5% of our cohort and 53.4% holding a university degree or higher (vs. 38.5% of the Australian population 25–29 years of age; two-proportions z-test chi-squared = 27.57, df = 1, $p < 0.001$).[27] Despite relatively high levels of education, overall unemployment rate was 21.3%, approximately four-fold higher than the Australian general population rate of 5.4%.[28]

Smoking and alcohol. Thirty-six percent were current smokers; three-fold higher than age-matched Australian population mean.[29] Hazardous alcohol use in specialist clinics was greater than in primary care (15.8% vs. 8.0%, Chi-square = 22.6; df = 2; < 0.001); however, remained lower than the general Australian population.[29]

Table 1. Gender Identity Distribution Among Specialist and Primary Care Clinics

	All $N = 540$	Endocrine specialist $N = 283$	Primary care $N = 257$	Overall p value
Trans female	196 (36.3%)	95 (33.6%)	101 (39.3%)	
Trans male	238 (44.1%)	165 (58.3%)	73 (28.4%)	
Nonbinary	99 (18.3%)	21 (7.4%)	78 (30.4%)	
Unassigned	7 (1.3%)	2 (0.7%)	5 (1.9%)	< 0.001

Number (proportion of the cohort) is reported. *p* Value refers to overall difference in gender identity proportions based on Fisher's exact test.

Clinical characteristics

Medical morbidities. Median Charlson Medical Comorbidity Score was 0 (0, 1). Individual medical characteristics are described in Table 2. Median overall blood pressure was within normal limits (125/80 mmHg); however, median BMI was in the overweight range 25.6 kg/m^2 (22.1, 30.9).

Psychiatric conditions. Around 88.3% had been assessed by a psychiatrist or psychologist experienced in gender dysphoria before commencement of gender-affirming hormone therapy. The prevalence of psychiatric conditions was high and the most commonly diagnosed conditions are outlined in Table 3. Of note, depression was prevalent in 55.7%, anxiety in 40.4%, ASD in 4.8% and ADHD in 4.3%, all higher than age-matched Australian population means (Fig. 2).[30,31]

Five individuals had diagnoses of both ASD and ADHD. Of individuals with ADHD, there were similar numbers who were birth-assigned males ($n = 12$) and birth-assigned females ($n = 11$). Conversely in individuals with ASD, there was a greater proportion of birth-assigned males [$n = 17$ (65%)] than birth-assigned females [$n = 9$ (35%)]. However, the proportion of ASD is not significantly different between birth-assigned males (8.7%) and birth-assigned females (3.8%; Chi-squared = 3.74, df = 1, $p = 0.053$).

Table 2. Medical Characteristics

	All	*N*
Age at first consultation (years)	27 (22, 36)	540
Duration of hormone therapy (months)	0 (0, 18)	457
Charlson medical comorbidity index	0 (0, 1)	540
Hypertension[a]	46 (11.5%)	540
Hypercholesterolemia[b]	56 (15.6%)	540
Ischemic heart disease	4 (0.7%)	540
Human immunodeficiency virus (HIV)	2 (0.4%)	540
Chronic obstructive airways disease	79 (14.6%)	540
Liver disease	25 (4.6%)	540
Venous thromboembolism	7 (1.5%)	540
Stroke	1 (0.2%)	540
Cancer/Malignancy	8 (1.5%)	540
Previous genital reassignment surgery	46 (8.5%)	540
Body mass index (kg/m^2)	25.6 (22.1, 30.9)	190
Systolic blood pressure (mmHg)	125 (120, 130)	397
Diastolic blood pressure (mmHg)	80 (75, 82)	394

Median (IQR) are shown or number (prevalence %) for categorical parameters. *N* = number of individuals for which data was available.
[a]A hypertension diagnosis was based on antihypertensive treatment.
[b]Hypercholesterolemia diagnosis was based on statin use.

Table 3. Prevalence of Psychiatric Conditions

	Australian population prevalence[a] %	All *N* = 540
Major depression	7.9%[b62]	301 (55.7%)
Anxiety	16.3%[b62]	218 (40.4%)
Bipolar disorder	1.8–3.6%[67]	18 (3.3%)
Post-traumatic stress disorder	6.4%[67]	24 (4.4%)
Obsessive compulsive disorder	1.9%[67]	11 (2.0%)
Borderline personality disorder	2.7%–6%[68]	35 (6.5%)
Other personality disorders	< 1.7%[68]	8 (1.5%)
Eating disorders	0.8–11.1%[69]	16 (3.0%)
Autism spectrum disorder	0.7%[31]	26 (4.8%)
Attention-deficit/ hyperactivity syndrome (ADHD)	1.1%[30]	23 (4.3%)

Number (proportion of the cohort) is reported.
[a]Australian population prevalence is based on median age of 27.
[b]Refers to prevalence rates for age group 25–34.

Thirty-two percent of individuals with ADHD were taking stimulant medication.

Gender-affirming hormone therapy regimens. Choice of hormone therapy varied widely. The most frequently used regimen for trans females was estradiol valerate combined with either spironolactone or cyproterone acetate and for trans males, intramuscular testosterone undecanoate injections (Table 4). Preferred agents were mirrored in individuals identifying as gender nonbinary.

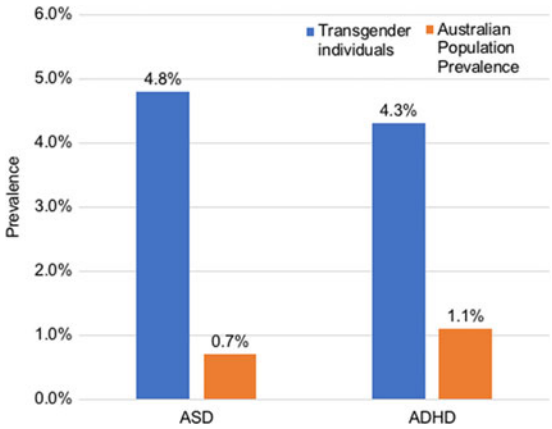

FIG. 2. Prevalence of ASD and ADHD in our cohort and the Australian adult population prevalence.[30,31] ADHD, attention-deficit/ hyperactivity disorder; ASD, autism spectrum disorder.

Gender affirmation surgery. Of 196 trans female individuals, 36 (18.4%) had undergone genital reassignment surgery (vaginoplasty and orchidectomy). Four (2.0%) had orchidectomy alone, 6 (3.1%) had breast augmentation, 5 (2.6%) had facial feminization surgery and 1 individual had a laryngeal shave procedure. Of 238 trans male individuals, 14 (5.9%) had undergone hysterectomy and 1 individual had phalloplasty. Mastectomy had been performed in 88 (40.0%) individuals. Of 99 individuals identifying as gender nonbinary, 1 individual (1.0%) had orchidectomy, 11 (12.1%) had mastectomy, and 1 (1.0%) had laryngeal shave.

Among individuals with ASD and/or ADHD, of 19 trans female individuals, 1 (5%) had vaginoplasty. Of 15 trans males, 5 had prior mastectomy (33%). No individuals who identified as gender nonbinary had any prior surgery.

Discussion

In this large cross-sectional study of adult transgender individuals, we report a rapid rise in demand for transgender health care, with more than 10 times the number in 2016 compared with 2011. Individuals identifying as gender nonbinary comprise 18.3% of the overall transgender cohort and greater numbers of trans male individuals are seen in endocrine practice. Despite few medical morbidities, smoking, unemployment, social disadvantage, and mental illness are highly prevalent which must be considered in the development of comprehensive multidisciplinary care for transgender Australians. Notably, the prevalence of ADHD, ASD, depression, and anxiety are higher in adult transgender individuals than age-appropriate Australian population mean.

Increasing demand

Due to fear of disclosure, differences in case definition[32] and a lack of studies involving population-based representative samples, the prevalence of gender dysphoria is inherently challenging to determine. Estimates report 0.1–0.6% of the population identify as gender variant.[33–35] Demand for gender clinics has risen several fold in many countries worldwide over the last decade.[4,36,37] It is not only demand for hormonal therapy, but gender-affirming surgery has also increased threefold between 2012–2014.[38] Our data mirror this worldwide trend, which is likely to be a result of increased societal acceptance of gender diversity, tolerance, and visibility of transgender individuals online and in the media. The concern is that current health care services

Table 4. Gender-Affirming Hormone Therapy Regimens Prescribed

	All	Proportion
Trans female individuals	*N* = 177	
Oral estradiol + antiandrogen[a]	77	43.5%
Oral estradiol	45	25.4%
Transdermal estradiol (patch/gel)	11	6.2%
Transdermal estradiol (patch/gel) + oral estradiol + antiandrogen[a]	10	5.6%
Combined oral contraceptive pill[b]	8	4.5%
Transdermal estradiol (patch/gel) + antiandrogen[a]	7	4.0%
Transdermal estradiol (patch/gel) + oral estradiol	3	1.7%
Antiandrogen	2	1.1%
Combined oral contraceptive pill[b] + antiandrogen[a]	2	1.1%
GnRH agonist subcutaneous implant	2	1.1%
GnRH agonist subcutaneous implant + oral estradiol	1	0.6%
Other[c]	9	5.1%
Trans male individuals	*N* = 218	
Testosterone undecanoate injection	160	73.4%
Testosterone enanthate injection	35	16.1%
Transdermal testosterone (solution/gel/cream)	18	8.3%
Testosterone undecanoate injection + transdermal testosterone (solution/gel/cream)	2	0.9%
Testosterone enanthate injection+ transdermal testosterone (solution/gel/cream)	1	0.5%
Testosterone enanthate injection + Testosterone ester mix injection	1	0.5%
Testosterone ester mix injection	1	0.5%
Gender nonbinary individuals	*N* = 51	
Birth-assigned females		
Testosterone undecanoate injection	15	29.4%
Transdermal testosterone (solution/gel)	12	23.5%
Testosterone enanthate injection	4	7.8%
Birth-assigned males		
Oral estradiol + antiandrogen[a]	11	21.6%
Oral estradiol	4	7.8%
Topical estradiol (patch) + oral estradiol + antiandrogen[a]	1	2.0%
Antiandrogen[a]	1	2.0%
Combined oral contraceptive pill	1	2.0%
Other[d]	2	3.9%

The total number refers to only individuals who were receiving gender-affirming hormone therapy. Number (proportion) is reported.
[a]Antiandrogen refers to cyproterone acetate, spironolactone, or bicalutamide.
[b]Ethinyl estradiol and levonorgestrel.
[c]Other refers to raloxifene + oral estradiol + antiandrogen ($n = 1$), oral estradiol + progesterone ($n = 2$), transdermal estradiol (patch) + antiandrogen + progesterone ($n = 1$), oral estradiol + antiandrogen + progesterone ($n = 2$), estradiol/progesterone cream + antiandrogen ($n = 1$), oral estradiol + low-dose transdermal testosterone ($n = 2$).
[d]Other refers to raloxifene + antiandrogen ($n = 1$), transdermal estradiol (patch) + antiandrogen + progesterone ($n = 1$).

will not be able to meet continuous increases in demand. Expansion of telehealth consultations may be a cost-effective strategy to provide specialized gender outreach services (in partnership with local primary care physicians) to the 30% of individuals residing in rural and regional locations.

Gender identity

Trans females traditionally outnumber trans males,[6,39] however, gender identity distributions observed in this study showed a shift. The endocrine specialist cohort demonstrated a reversal of this ratio with three times as many trans males as trans females presenting for hormone therapy. This is likely related to new restrictions by the Australian Pharmaceutical Benefits Scheme introduced in early 2015, which require a specialist endocrinologist, sexual health physician, or urologist consultation to access government-subsidized testosterone therapy. It is also possible that our results may reflect changing gender proportions within the transgender community at large. Indeed, this latter argument is supported by the ongoing multinational ENIGI study recently documenting higher frequencies of trans male individuals in their combined study population[40] and in Canadian and Dutch gender clinics.[41]

We report a high prevalence of nonbinary gender identity (30%) among our primary care population. There are no peer-reviewed publications examining the prevalence of nonbinary gender identity, however, published online surveys of transgender populations report between 5% and 13% identity as such.[42,43] Identification as a nonbinary gender, of which there are many terms with which individuals identify (i.e., genderqueer, gender fluid, agender), may be emerging

with increasing recognition of gender as a spectrum and societal acceptance in challenging conventional gender stereotypes.

Sociodemographic characteristics

Despite relatively high levels of education, unemployment rates of 21.3% were high in this relatively young cohort, four-fold higher than the Australian general population unemployment rate of 5–6%.[44] High rates of unemployment among transgender individuals (33–35%) have also been reported in the United States of America and Spain.[45,46] There are a range of potential contributing factors to unemployment, including fear of disclosure, employer discrimination, conflicting gender codes or names on qualifications or references, and mental health conditions. Of concern, young transgender individuals reporting difficulties obtaining employment had higher rates of suicide attempts and mental health conditions than those who did not.[47] Smoking rates in the transgender community are high, but similar to rates among Australians with depression and anxiety, which may reflect smoking being a means to relieve psychiatric symptoms. Smoking and being overweight are both cardiovascular risk factors affecting this relatively young population, and given the uncertain long-term cardiovascular effects of testosterone or estradiol therapy, proactive cardiovascular risk reduction should be considered in all transgender individuals.

Clinical characteristics, ASD, and ADHD

We report a high prevalence of ADHD (4.1%) in our cohort, which is higher than adult Australian population prevalence of 1.1–2.7%.[30] We interestingly observed a similar male to female ratio in those with ADHD, which is in contrast to the male predominance observed in the general population.[48] However, it has been suggested that underdiagnoses may occur among females in the community,[48] and symptoms, which are typically more commonly exhibited by women, such as inattention, may not be recognized as symptoms of ADHD.[49] There has only been one other small study suggesting a higher prevalence of ADHD in adult transgender individuals ($n = 54$).[19] Notably, this was a convenience sample from a paid online survey, which has multiple limitations, including a bias toward young internet users, and is unlikely to be representative of population-based samples or transgender cohorts.[19] Potentially, misdiagnoses of ADHD may be a contributing factor. Both ASD and ADHD can severely compromise health and wellbeing, particularly if left undiagnosed.[30,50] Symptoms such as attention difficulties, deficits in communication and social skills, obsessional interests, and stereotyped behavior can significantly impact assessment of gender dysphoria, understanding of health information, and engagement in clinical care.[51] These factors may potentially explain fewer individuals with ASD or ADHD undergoing gender-affirming surgery than transgender individuals in our study. Gender nonconforming youth often present with externalizing behaviors,[52] and symptoms such as attention deficit, impulsivity, and hyperactivity may be explained in part by ASD rather than ADHD, although distinguishing the two diagnoses is usually achievable.[53] While contentious and lacking supportive data, it has been suggested that endocrine disruptors such as prenatal exposure to phthalates[54] or antidepressants[55] may be an explanation for the increase of ADHD and ASD and relationship with gender variance. There is evidence that phthalates may play a role in reproductive development *in utero* and sex steroid hormone levels.[56,57] Sex hormones may also play a role in the development of these conditions. Familial and twin studies have shown that approximately 50–72% of contributing genetic factors overlap in ADHD and ASD.[58] There may potentially be shared genetic or epigenetic underpinnings or neurodevelopmental links among gender identity, ADHD, and ASD.[59] Such hypotheses and observations will hopefully provide impetus to further study the links among ADHD, ASD, and gender.

The prevalence of ASD of 5% in our adult cohort is also significantly higher than Australian adult population prevalence rates of <1%.[60] Three published cross-sectional analyses of clinical chart data have described similar rates of prior diagnoses of ASD ranging from 6% in adults and 7–13.3% in children and adolescents with gender dysphoria.[12,13,16] Many more studies have used surrogate autism screening tools and reported scores suggestive of ASD, however, it is possible that high levels of social anxiety related to minority stress or potential peer or family rejection may lead to falsely positive screening tests.[61] Prospective controlled studies with rigorous diagnostic assessments for ASD, ADHD, and gender dysphoria are required.

Not surprisingly, we report an extremely high prevalence of diagnosed depression and anxiety, which is 10-fold higher than the general population[62] and is comparable with previous studies among transgender populations.[6,8,46,63] There are greater risks of depression,

anxiety, and suicide reported among individuals with ADHD and ASD.[64,65] Although there are many contributing factors to this, including discrimination and difficulties accessing gender-affirming treatments, our results exemplify the need for multidisciplinary coordinated care[66] and mental health support for transgender individuals, including availability of services to treat, monitor, and effectively support individuals with ASD and ADHD. As both ASD and ADHD are complex conditions with variable functional challenges, provision of information and gender-affirming care needs to be tailored to different learning styles specific to the individual. Clinicians may need to employ a range of different tools and approaches to account for factors such as inattention, lack of organization, and communication difficulties. Additionally, psychosocial interventions to develop interpersonal skills, increase self-esteem, and improve social and peer support may benefit individuals who struggle with social aspects of gender transition.

There were a number of key limitations to this cross-sectional retrospective audit. While we attempted to capture primary and specialist care clinics in the state of Victoria, we are uncertain of referral patterns in other states and territories of Australia, however, given the worldwide trends reported, it is likely similar rises in demand for transgender health are being seen. In addition to limitations inherent in the study design, including lack of a control group and missing data, we collected diagnoses listed in medical records, which while entered by medical practitioners during initial consultations, are largely based on self-reported clinical history and we did not have details regarding the specific diagnostic process leading to the diagnosis of ADHD or ASD. We also did not have temporal data on the effect of gender-affirming hormone therapy on mental health conditions such as depression. We also did not have data on suicidality or contributing factors to depression or anxiety. Nonetheless, this is a large real-life clinical cohort and our findings warrant further confirmation in prospective studies. Until further data are available, decreasing mental health burden and improving quality of life should be made a priority. Comprehensive multidisciplinary gender services may be best placed to meet the complex mental health needs of this socially disadvantaged group.

Conclusion

There is a rising demand for transgender health services, and we observe an increased prevalence of depression, anxiety, ADHD, and ASD higher than the general population. A coordinated multidisciplinary approach to transgender health care, including psychosocial interventions to support mental health and neurobehavioral conditions in adults in parallel to gender-affirming treatments are essential to meet the needs of this socially disadvantaged cohort. There are many future research priorities, including studies to assess and understand the links between neurobehavioral conditions and gender dysphoria, clinical trials to provide evidence-based treatment pathways and studies to evaluate optimal models of health service provision to improve quality of life and minimize mental health burden. Until further evidence is available, provision of health services need to be tailored to the specific health needs of transgender individuals with a focus on continual quality improvement as new knowledge and data arise.

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Author Disclosure Statement

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Abbreviations Used

ADHD = attention-deficit/hyperactivity disorder
ASD = autism spectrum disorder
BMI = body mass index

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Relationship Between Serum Estradiol Concentrations and Clinical Outcomes in Transgender Individuals Undergoing Feminizing Hormone Therapy: A Narrative Review

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Abstract

Transgender, including gender diverse and nonbinary, individuals are treated with estradiol with or without antiandrogen to align their physical appearance with their gender identity, improve mental health and quality of life. Consensus guidelines give target ranges for serum estradiol concentration based on premenopausal female reference ranges. However, limited studies have evaluated the relationship between serum estradiol concentrations and clinical outcomes in transgender individuals undergoing feminizing hormone therapy. The available evidence has not found that higher serum estradiol concentrations, together with suppressed testosterone, enhance breast development, or produce more feminine changes to body composition. However, ensuring testosterone suppression appears to be an important factor to maximize these physical changes. Higher serum estradiol concentrations have been associated with higher areal bone mineral density. Although the resultant long-term clinical implications are yet to be determined, this could be a consideration for individuals with low bone mass. The precise serum estradiol concentration that results in adequate feminization without increasing the risk of complications (thromboembolic disease, cholelithiasis) remains unknown. Further prospective trials are required.

Keywords: body composition; bone; breast; estradiol; transgender

Introduction

Transgender, including gender diverse and nonbinary, individuals who seek feminization are often treated with estradiol with or without antiandrogen to increase serum estradiol concentration and decrease serum testosterone concentration into the reference ranges for premenopausal women. Physical changes, including softening of skin, a decrease in facial and body hair, breast development, and feminine changes to body composition, develop within months although maximal effects may take 2–3 years.[1]

Consensus guidelines give recommendations for serum estradiol concentration targets to permit titration of estradiol therapy.[1–3] The 2017 Endocrine Society Clinical Practice Guidelines recommend maintenance of serum estradiol concentrations between, and not exceed, 100–200 pg/mL (367–734 pmol/L) and testosterone concentrations < 50 ng/dL (1.7 nmol/L).[1] These values are derived from sex steroid concentrations in premenopausal women and represent a surrogate target to enable suppression of testosterone while minimizing supraphysiological estradiol concentrations. However, no study has been performed to establish optimal estradiol concentrations to promote feminization in transgender individuals undergoing feminizing hormone therapy. When considering optimal serum estradiol concentrations, adequate feminization must be weighed against potential risks, given that escalating oral

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estradiol dose has been associated with an increased thromboembolic risk in the menopausal hormone therapy literature.[4]

Given the uncertainty regarding estradiol concentration targets in transgender individuals undergoing feminizing hormone therapy, we undertook a narrative review to establish the relationship between serum estradiol concentrations and clinical outcomes. Herein, we present a summary of the literature regarding the relationship between serum estradiol concentrations and breast development, body composition, and bone health in transgender individuals. We also consider risks associated with escalating estradiol dose and serum estradiol concentration. MEDLINE, EMBASE, and PsycInfo were searched using MeSH terms and text words for transgender, estradiol, breast, body composition, and bone. No randomized controlled trials were found, so data have been obtained from prospective cohort, retrospective cohort, and cross-sectional studies. We also searched the references listed in relevant publications.

Breast development

Breast development is a key clinical outcome for many transgender individuals. However, breast development is often modest,[5–8] and many individuals seek surgical breast augmentation.[6,9] Two studies have reported the influence of serum estradiol concentration on breast development in transgender individuals.

de Blok et al. performed a 12-month prospective study as part of the European Network for the Investigation of Gender Incongruence (ENIGI) to evaluate breast development in 229 transgender individuals newly commencing gender-affirming hormone therapy (GAHT).[5] Breast development, as measured by changes in breast-chest circumference and cup size, was modest and predominantly occurred within the first 6 months of GAHT. Mean breast-chest difference increased to 7.9 ± 3.1 cm after 12 months, with nearly half of participants having less than AAA cup size.

Serum estradiol concentration, taken as an average of two values performed at months 3 and 12, did not predict breast development after 12 months of GAHT (Table 1). Only the highest quartile (mean serum estradiol concentration 452 pmol/L in Amsterdam and 567 pmol/L in Ghent) reached serum estradiol concentrations recommended in Endocrine Society guidelines. Testosterone was suppressed in 92% of individuals, so further analyses evaluating the influence of serum testosterone concentration could not be performed.

Breast development was also analyzed by Meyer et al., who reported a retrospective cohort study involving 155 transgender individuals.[10] Similar to the previous study, the authors also reported breast development by breast-chest difference but also by Tanner stage. Median breast-chest difference measured 8.5 ± 5 cm and Tanner stage 4 ± 1 at 3–4 years with estradiol concentration 342 ± 382 pmol/L. Serum estradiol concentration had no significant influence on breast development (Spearman correlation $[\rho] = -0.117$, $p = 0.316$) (Table 1). Owing to its retrospective nature, there was greater variability in the hormone regimen used, and 17% of individuals were not treated with antiandrogen therapy, which permitted further analysis of the influence of serum testosterone concentration. Both serum testosterone concentration and free androgen index (FAI) were significantly negatively correlated with the level of Tanner stage (testosterone: $\rho = -0.398$, $p < 0.001$; FAI: $\rho = 0.346$, $p = 0.004$).

Older studies have also reported the influence of estradiol dose on breast development. One cross-sectional analysis of 38 transgender individuals reported higher breast hemicircumference with higher estradiol doses,[11] whereas a subsequent longitudinal study enrolling 60 individuals did not.[12] It should be noted that these studies utilized ethinyl estradiol and conjugated estrogens, which are no longer recommended as part of feminizing hormone regimens given inability to measure serum estradiol concentrations and increased risk of thromboembolic disease.[1,13]

In summary, serum estradiol concentration has not been found to be associated with breast-chest difference or Tanner stage in transgender individuals. However, ensuring suppression of testosterone might be an important factor to promote maximal breast development. Limited data are available examining bra cup size or development of the nipple-areolar complex and this requires further study.

Body composition

Several prospective studies have examined changes in body composition after initiation of GAHT in transgender individuals.[14–26] Typical changes include a reduction in lean mass and increase in fat mass, particularly gynoid fat.[27,28] However, the current literature is limited by a lack of controlled studies and only one study has examined the relationship between changes in body composition and serum estradiol concentration.

Klaver et al. reported changes in body composition using whole-body dual-energy x-ray absorptiometry

Table 1. Influence of Serum Estradiol Concentration on Clinical Outcomes in Transgender Individuals Undergoing Feminizing Hormone Therapy

Reference	*Country*	*Study type*	*Duration*	*Number of individuals*	*Results*
Breast development					
de Blok et al.[5]	Netherlands, Belgium, and Italy (ENIGI)	Prospective, cohort	12 months	229	Serum estradiol concentration did not predict breast development (first quartile, 3.6 cm [95% CI: 2.7–4.5], second quartile, 3.2 cm [95% CI: 2.3–4.2], third quartile, 4.4 cm [95% CI: 3.5–5.3], and fourth quartile, 3.6 cm [95% CI: 2.7–4.5])
Meyer et al.[10]	Germany	Retrospective, cohort	Up to 3–4 years	155	Estradiol concentration had no significant influence on breast development (Spearman correlation [ρ] = −0.117, p = 0.316)
Body composition					
Klaver et al.[14]	Netherlands and Belgium (ENIGI)	Prospective, cohort	12 months	179	No association between mean serum estradiol concentration and body fat or lean body mass (p = not reported)
Klaver et al.[26]	Netherlands	Retrospective, cohort	Mean 7.5 years	71	Serum estradiol concentration increased from 25 to 121 pmol/L after commencement of estradiol. Percentage of lean body mass increased 3%,[1,5] percentage of total fat mass decreased −3% (−5,−1), and WHR decreased −0.02 (−0.04, 0.01) after commencement of estradiol
Bone health					
Lapauw et al.[36]	Belgium	Cross-sectional	N/A	23	Serum sex steroid concentrations not associated with pQCT parameters (p > 0.18)
Van Caenegem et al.[20]	Belgium (ENIGI)	Prospective, cohort	12 months	49	Serum estradiol concentration not associated with changes in BMD or pQCT parameters (data not shown)
Wiepjes et al.[30]	Netherlands and Belgium (ENIGI)	Prospective, cohort	12 months	231	Amsterdam: Estradiol concentration correlated with LS (per 100 pmol/L: +0.95%, 95% CI: 0.34 to 1.56, p = 0.003), TH (per 100 pmol/L: +0.48%, 95% CI: 0.04 to 0.93, p = 0.034), and FN (per 100 pmol/L: +0.83%, 95% CI: 0.31 to 1.36, p = 0.002) BMD change Ghent: Estradiol concentrations correlated with LS (per 100 pmol/L: +0.87%, 95% CI: 0.27 to 1.47, p = 0.005), but not with TH (per 100 pmol/L: +0.40%, 95% CI: −0.12 to 0.92, p.0 = 126) or FN (per 100 pmol/L: +0.09%, 95% CI: −0.67 to 0.85, p = 0.814) BMD change
Wiepjes et al.[34]	Netherlands (ACOG)	Retrospective, cohort	Up to 10 years	711	Higher estradiol tertiles were associated with higher LS BMD than lower estradiol tertiles: Second tertile vs. first tertile +0.033 (0.006 – 0.059) Third tertile vs. first tertile +0.076 (0.050 – 0.103) Third tertile vs. second tertile +0.044 (0.018 – 0.070)
Vlot et al.[33]	Netherlands and Belgium (ENIGI)	Prospective, cohort	12 months	121	Sclerostin decreased in all but the lowest estradiol quartile ($p \leq 0.05$ vs. other quartiles) No significant differences were seen with CTx, P1NP or ALP between estradiol quartiles
Wiepjes et al.[35]	Netherlands (ACOG)	Retrospective, cohort	Median 8 years (aged <50), 19 years (aged ≥50)	2023 (1089 aged <50, 934 aged ≥50)	On univariable analyses, no association was found between estradiol concentration and fracture risk (per 10 pmol/L: OR = 0.99, 95% CI: 0.97–1.02)

ACOG, Amsterdam Cohort of Gender Dysphoria; ALP, alkaline phosphatase; BMD, bone mineral density; CI, confidence interval; CTx, C-terminal telopeptide of type 1 collagen; ENIGI, European Network for the Investigation of Gender Incongruence; FN, femoral neck; LS, lumbar spine; OR, odds ratio; P1NP, procollagen type 1 N propeptide; pQCT, peripheral quantitative computed tomography; TH, total hip; WHR, waist-hip ratio.

(DXA) after commencement of GAHT in a 12-month prospective observational study that enrolled 179 transgender adults.[14] Resultant changes in body composition included increased body fat, more predominant at the gynoid region, and a decrease in waist-to-hip ratio. Mean serum estradiol concentration measured at months 3 and 12 was not found to be associated with changes in body fat or lean body mass.[14]

The use of gonadotropin-releasing hormone agonists (GnRHa) with subsequent commencement of estradiol in transgender adolescents allows further evaluation of changes directly attributable to estradiol. Klaver et al. reported changes in body composition in a retrospective study involving 71 transgender adolescents.[26] GnRHa were used to achieve puberty suppression, with GAHT commenced from 16 years of age. At 22 years of age, body composition parameters, including waist-hip ratio, total body fat, and lean body mass, were more closely aligned with that of cisgender women.

Larger changes in total body fat (+6% [4, 7] vs. +3% [1, 5]) and lean body mass (−6% [−7, −4] vs. −3% [−5, −1]) were seen during GnRHa monotherapy than after commencement of estradiol. This could suggest that suppression of testosterone has a greater impact on body composition than estradiol. However, it remains unclear if these changes are directly attributable to testosterone suppression or the sex steroid-deficient state achieved during GnRHa therapy.

In summary, serum estradiol concentration has not been found to be associated with changes in body composition in transgender adults. Although changes in body composition are seen after sequential commencement of estradiol in transgender adolescents, these changes were smaller than those seen after the initial commencement of GnRHa monotherapy.

Bone health

Despite reports of low bone mass in transgender individuals before initiation of GAHT,[20,29] prospective studies[20,22,30,31] and a meta-analysis[32] have demonstrated improvements in areal bone mineral density (BMD) after commencement of GAHT. Several studies have examined the association between serum estradiol concentration and bone outcomes in transgender individuals.

Two prospective studies in the ENIGI cohort have evaluated changes in areal BMD and bone turnover markers in transgender individuals for the first 12 months of GAHT. Both studies evaluated the correlation between bone parameters and serum estradiol concentration, taken as a mean of values performed at months 3 and 12. Wiepjes et al. reported changes in areal BMD in 231 transgender individuals and found that absolute BMD increased at the lumbar spine (LS) (+3.67%, 95% confidence interval [CI]: 3.20 to 4.13, $p < 0.001$), total hip (TH) (+0.97%, 95% CI: 0.62 to 1.31, $p < 0.001$), and femoral neck (FN) (+1.86%, 95% CI: 1.41 to 2.31, $p < 0.001$) for 12 months.[30]

Estradiol assays differed between sites so cohorts from Amsterdam and Ghent were reported separately. In Amsterdam, serum estradiol concentration was found to correlate with LS, TH, and FN BMD change, whereas in Ghent serum estradiol concentration correlated with LS BMD change but not TH or FN (Table 1).

Vlot et al. evaluated changes in markers of bone metabolism in 121 transgender individuals newly commencing GAHT.[33] They found that alkaline phosphatase decreased in 19% (95% CI: −21 to −16), C-terminal telopeptide of type 1 collagen (CTx) decreased in 11% (95% CI: −18 to −4), and sclerostin decreased in 8% (95% CI: −13 to −4) of individuals after 12 months of GAHT (Table 1). Serum estradiol concentration was reported in quartiles (first quartile 115 pmol/L, second quartile 192 pmol/L, third quartile 280 pmol/L, and fourth quartile 527 pmol/L) in this analysis. The lowest estradiol quartile showed a slight increase in sclerostin concentration, whereas sclerostin decreased in the other quartiles. There was no association between the other markers of bone metabolism and serum estradiol concentration. This could imply that the serum estradiol concentrations achieved in the lowest quartile could be too low to result in reduced bone turnover.

Two retrospective cohort studies from the Amsterdam Cohort of Gender Dysphoria (ACOG) have aimed to establish the long-term changes in areal BMD and fracture risk in transgender individuals. Wiepjes et al. reported changes in absolute BMD and Z-score as measured by DXA in 711 transgender individuals up to 10 years after commencement of GAHT.[34] The mean sex steroid concentrations in this study were established by averaging results from laboratory measurements after 1, 2, 5, and 10 years of GAHT and reported in tertiles. Only individuals in the third tertile achieved serum estradiol concentrations recommended in Endocrine Society Clinical Practice Guidelines.

After 10 years of GAHT, LS BMD was not different from baseline (+0.006 g/cm^2 [−0.005 to +0.017 g/cm^2]). However, in the cohort that achieved serum estradiol

concentrations in the highest estradiol tertile (mean 442 pmol/L), an increase in LS BMD was observed ($+0.044$ g/cm^2 [$+0.025$ to $+0.063$ g/cm^2]), whereas there was a decrease in those in the lowest tertile (mean 118 pmol/L: -0.026 g/cm^2 [-0.044 to -0.009 g/cm^2]). BMD was stable in the second tertile (mean 238 pmol/L: $+0.002$ g/cm^2 [-0.016 to $+0.0021$ g/cm^2]). There was no difference in the change in LS BMD between individuals with suppressed versus not suppressed testosterone.

Wiepjes et al. also established the fracture incidence of transgender individuals treated with long-term GAHT.[35] Their study included 2023 transgender individuals; 1089 < 50 years of age treated with GAHT for a median of 8 years and 934 individuals age 50 years or older treated with GAHT for a median of 19 years. In total 2.4% of younger and 4.4% of older transgender women sustained a fracture. It should be noted that fracture data were obtained from a database of emergency room presentations and may not represent minimal trauma fractures. Compared with age-matched cisgender men, older transgender women had a higher prevalence of fracture (odds ratio [OR] = 1.90, 95% CI: 1.32–2.74). Laboratory measurements were available in 66% of individuals. On univariable analyses, no association was found between serum estradiol concentration and fracture risk (per 10 pmol/L: OR = 0.99, 95% CI: 0.97–1.02).

Two studies have established volumetric BMD using peripheral quantitative computed tomography (pQCT) in transgender individuals. Serum estradiol concentration at 12 months was not associated with BMD or pQCT parameters in a cohort of 49 transgender individuals.[20] Similarly, serum estradiol concentration was not associated with pQCT parameters in a cross-sectional analysis of 23 transgender individuals at least 3 years postgender-affirming surgery.[36] Both studies are limited by small numbers of participants and estradiol concentration measured at one timepoint.

In summary, higher serum estradiol concentrations have been associated with higher areal BMD in some studies of transgender individuals. Based on current data, if serum estradiol concentration is maintained > 200–250 pmol/L (54–68 pg/mL), serum bone turnover markers are reduced and LS BMD remains stable. Small studies have not found associations between pQCT parameters and serum estradiol concentration.

Risks of escalating estradiol dose/concentration

The risks of escalating estradiol dose to achieve higher serum estradiol concentrations must be weighed against potential adverse events. Higher oral estradiol doses (defined as > 1 mg estradiol,[4,37] or > 2 mg estradiol or 0.625 mg conjugated equine estrogens[38]) have been associated with an increased risk of venous thromboembolism with menopausal hormone therapy. However, this has not been demonstrated with high-dose (> 50 mcg/24 h) transdermal preparations[4,37,38] apart from one nested case–control study in which there was an increased risk of stroke in women treated with transdermal estradiol > 50 mcg/24 h compared with low-dose estradiol.[39]

Higher oral estradiol dose has also been associated with a higher risk of cholelithiasis in postmenopausal women,[40] but there have not been reports of an increased risk of cholelithiasis in transgender individuals undergoing feminizing hormone therapy. It is also important to acknowledge that the literature from which this is derived is based on doses often much lower than those administered to transgender individuals, and include studies involving conjugated equine estrogens that are not recommended for GAHT.[1]

Higher endogenous serum estradiol concentrations have also been associated with an increased risk of peripheral arterial disease in men[41] and breast cancer in postmenopausal women.[42] One cohort study of elderly men found an association between higher serum estradiol concentrations and cerebrovascular disease in men,[43] but no association was found in a subsequent meta-analysis.[44] Importantly, higher endogenous serum estradiol concentrations have been associated with lower coronary artery calcium score in postmenopausal women.[45]

Contribution from testosterone suppression

Current guidelines recommend increasing serum estradiol and decreasing serum testosterone into the respective reference ranges of premenopausal women. It is, therefore, difficult to dissect the relative contributions of testosterone suppression from the increases in serum estradiol concentration. Published prospective studies from the ENIGI cohort prescribe cyproterone acetate 25–50 mg daily as antiandrogen therapy,[46] which results in testosterone suppression in the majority of individuals.[5] Lower doses of cyproterone acetate result in adequate testosterone suppression.[47] Importantly, more adequate suppression of serum testosterone concentration has been associated with enhanced breast development as measured by Tanner stage.[10] Similarly, greater changes in body composition are seen in transgender adolescents treated with GnRHa monotherapy than after subsequent commencement of estradiol.[26]

Limitations of current evidence

The current literature is limited by a small number of observational trials. These studies have based the estradiol concentration from the average of a limited number of serum estradiol concentration measurements with variability in the assay used. This is important given the imprecision of the estradiol immunoassay, particularly at low estradiol concentrations.[48] It should also be noted that only individuals in the highest quartile or tertile of serum estradiol concentration in the prospective studies achieved concentrations in the range recommended in the Endocrine Society guidelines.[1] The relative contribution of serum estradiol concentration on physical feminization in transgender adults is unknown. Similarly, given that most individuals have a suppressed serum testosterone concentration, the current evidence cannot distinguish the relative contributions of suppressed testosterone and serum estradiol concentration achieved.

Future directions

There is a need for prospective trials evaluating different serum estradiol concentration targets with clinical and radiological features of feminization in larger cohorts of transgender individuals. Ideally, serum estradiol concentration should be measured through liquid chromatography–mass spectrometry at more frequent timepoints. Although sex steroid concentrations have not been found to correlate with sexual desire[49] or anger[50] in transgender individuals undergoing feminizing hormone therapy, the influence of serum estradiol concentration on other end-points such as psychological distress or gender dysphoria should also be considered.

Conclusion

Limited uncontrolled prospective evidence has not found that higher serum estradiol concentrations with adequate testosterone suppression enhances breast development or produces more feminine changes to body composition in transgender adults. However, higher serum estradiol concentrations have been associated with higher areal BMD and could be considered in individuals with low bone mass. The precise serum estradiol concentration that results in adequate feminization without increasing the risk of complications remains unknown. Prospective studies with various serum estradiol concentration targets and clinical features of feminization are required.

Authors' Contributions

B.J.N. reviewed the literature and drafted and revised the article. A.S.C. provided supervision and revised the article.

Author Disclosure Statement

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Abbreviations Used

ACOG = Amsterdam Cohort of Gender Dysphoria
ALP = alkaline phosphatase
BMD = bone mineral density
CI = confidence interval
CTx = C-terminal telopeptide of type 1 collagen
ENIGI = European Network for the Investigation of Gender Incongruence
DXA = dual-energy x-ray absorptiometry
ENIGI = European Network for the Investigation of Gender Incongruence
FN = femoral neck
GAHT = gender-affirming hormone therapy
GnRHa = gonadotropin-releasing hormone agonists
LS = lumbar spine
OR = odds ratio
P1NP = procollagen type 1 N propeptide
pQCT = peripheral quantitative computed tomography
TH = total hip
WHR = waist-hip ratio

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ORIGINAL PAPER

Prevalence of Autism Spectrum Disorder and Attention-Deficit Hyperactivity Disorder Amongst Individuals with Gender Dysphoria: A Systematic Review

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Abstract
Autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) can compromise health and may be more prevalent amongst individuals with gender dysphoria (GD). Symptoms such as attention or social difficulties can impact assessment of GD, understanding of health information, and engagement in clinical care. To ensure neurodevelopmental conditions are adequately considered in gender health services, we aimed to systematically review the literature examining the prevalence of ASD and ADHD amongst individuals with GD. In this systematic review based on the PRISMA guidelines. MEDLINE and PsycINFO databases were searched for studies examining the prevalence of ASD and/or ADHD in individuals with GD or investigated the rate of GD in cohorts with ASD or ADHD. All English peer-reviewed publications were included. The search strategy identified 179 studies. After applying exclusion criteria, a total of 30 studies were identified, 22 studies which examined the prevalence of ASD or ADHD in people with GD. A further 8 studies examined the reverse; prevalence of GD in people with ASD. The few studies employing diagnostic criteria for ASD suggest a prevalence of 6–26% in transgender populations, higher than the general population, but no different from individuals attending psychiatry clinics. Few studies examine prevalence of ADHD. Low-level evidence exists to suggest a link between ASD and GD. Further population-based and controlled studies using diagnostic criteria for ASD and ADHD are required.

Keywords Transgender persons · Gender dysphoria · Attention-deficit hyperactivity disorder · Autism disorders

Introduction

Transgender healthcare services are in higher global demand than ever before (Cheung et al. 2018; Delahunt et al. 2018). In response, gender health services are swiftly expanding and being redesigned. This development presents a critical opportunity to tailor health care provision to specific health needs and alleviate the significant mental health burden associated with gender dysphoria (GD). Compelling evidence indicates a high prevalence of depression and anxiety amongst individuals with GD (Heylens et al. 2014; Reisner et al. 2015, 2016); furthermore, neurodevelopmental conditions such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) may well be more common in transgender individuals (Dawson et al. 2017; Gunter Heylens et al. 2018; Jones et al. 2012; Pasterski et al. 2014).

Both ASD and ADHD can severely compromise health and wellbeing, particularly if left undiagnosed (Ebejer et al. 2012; Simonoff et al. 2008). Symptoms such as attention difficulties, deficits in communication and social skills, obsessional interests, and stereotyped behaviour can significantly impact assessment of GD, understanding of health information, and engagement in clinical care (American Psychiatric Association 2013).

There is a widely held opinion of clinicians that there is an over-representation of neurodevelopmental conditions amongst individuals with GD and when the evidence to

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support this belief was questioned in a recent essay, vigorous debate ensued (Strang et al. 2018; Turban and van Schalkwyk 2018b; van der Miesen et al. 2018a). As such, we sought to review the updated evidence to investigate the prevalence of ASD and additionally for ADHD amongst individuals with GD in order to ensure such conditions are adequately considered in the unfolding design of gender health services and to better serve our patients.

Methods

Preferred reporting items for systematic review and meta-analysis (PRISMA) reporting guidelines were used in the development of this systematic review (Liberati et al. 2009).

Eligibility Criteria

All levels of evidence were included in this review, provided that the report was published in a peer-reviewed journal and in the English language. Qualitative studies and case reports were excluded as prevalence data were not able to be obtained.

Information Sources and Search Strategy

The first author consulted an expert reference librarian to design and conduct the electronic database search with input from the last author. Eligible studies were identified by searching the electronic databases Ovid MEDLINE® and Ovid PsycINFO® from inception to 30th September 2019. Controlled vocabulary supplemented with keywords were used to define the population (transgender individuals), and outcome of interest (autism spectrum disorder, Aspergers syndrome or attention deficit hyperactivity disorder).

Relevant papers were elicited by searching article titles and abstracts for transgender terms (*transgender, gender dysphori*, transsexual*, gender identity disorder*) combined with relevant neurodevelopmental terms (*autism spectrum disorder, autism, Aspergers syndrome, adhd, attention deficit hyperactivity disorder*) using the Boolean OR and AND operators. Inclusion criteria were studies assessing incidence of autistic traits, ASD, or ADHD amongst cohorts with GD. We also reviewed the reverse, GD in cohorts of individuals with ASD and/or ADHD. As original prevalence data could not be inferred from papers not in English, review articles, and case reports, these were excluded. A search of reference lists for articles pertaining to the topic elicited five further articles. In total, 30 studies were identified. A flow diagram in Fig. 1 illustrates the search process.

Study Selection

Our full search strategy is outlined in Fig. 1.

Data Collection

Data was collected via an electronic form to capture the data items listed below.

Data Items

Participant Characteristics

Age, presence of GD, transgender, autism spectrum disorder or attention deficit hyperactivity disorder, birth-assigned sex, current gender identifier.

Study Characteristics

Method utilised (diagnostic vs. screening), recruitment method, sample size.

Control or Comparison Population

Age, recruitment method, birth-assigned sex, presence of psychiatric disorder.

Outcomes

Prevalence of ASD or ADHD in individuals with GD.

Statistical Results

Adjusted and unadjusted prevalence or incidence estimates, number of patients, age of patients.

Results

174 studies were identified using MEDLINE, and PsycINFO and 5 additional studies were identified from bibliographic references. 110 studies remained after duplicates were removed. After screening title and abstracts, 53 were removed due to lack of relevance, and 2 for being in a language other than English. When the full-text articles were reviewed for eligibility, studies which could not comment on prevalence were removed, including 9 case studies, 2

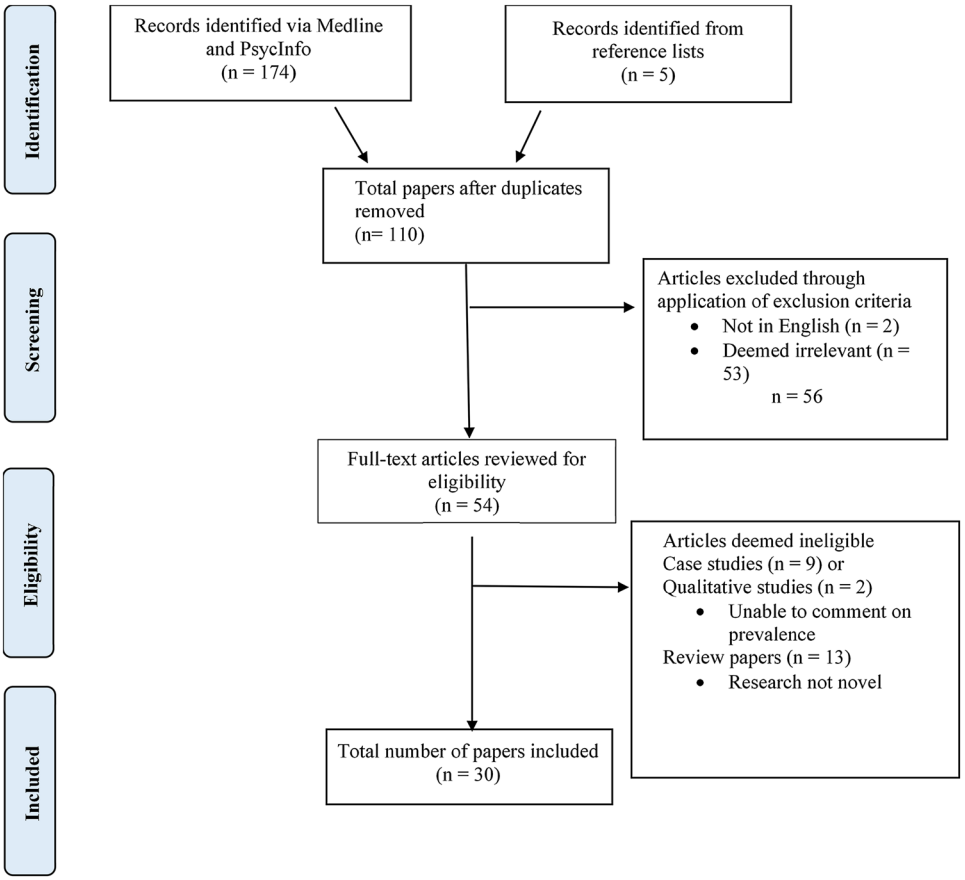

Fig. 1 Search process

qualitative studies, and 13 review papers. A summary of all the 30 identified remaining studies appears in Table 1.

Prevalence of ASD in Individuals with GD

Twenty-one of the identified papers described the prevalence of ASD, or autistic traits, within cohorts of individuals with GD. Table 1 groups studies according to age of study population, as this influences measures used by researchers and allows for ease of comparison. Prevalence ranged widely depending on the measures and cut-offs used. It is important to note that only 10 of the 21 papers included participants assessed using diagnostic measures. In a clinical chart review of 532 adults with GD, 6% had a prior diagnosis of ASD (Gunter Heylens et al. 2018). In children and adolescents referred to gender clinics, a cross-sectional analysis (n = 204) found 7.8% met diagnostic criteria for ASD (de Vries et al. 2010), and 13.3% had been diagnosed with ASD in a clinical chart review (n = 218) of children and adolescents attending a UK gender service (Holt et al. 2016). When measuring parameters such as social shortcomings, far higher rates of positive screening tests for ASD were observed; ranging from 6% to 68% (Table 1).

Prevalence of ADHD in Individuals with GD

Prevalence of ADHD has been assessed in four cross-sectional analyses (Cheung et al. 2018; Dawson et al. 2017; Holt et al. 2016; Kaltiala-Heino et al. 2015). A clinical chart review found that 8.3% of children and adolescents (n = 218) referred to a gender service had a prior diagnosis of ADHD (Holt et al. 2016). Amongst adults, in a convenience sample of 54 transgender adults participating in an online survey, 20.4% self-reported a prior diagnosis of ADHD (Dawson et al. 2017). More recently, a 2019 study reviewing electronic medical records revealed a prevalence rate of ADHD in 4.3% of transgender adults (Cheung et al. 2018).

GD in Individuals with ASD or ADHD

Whilst not the primary focus of the review, a summary of studies addressing the reverse; GD amongst individuals with neurodevelopmental conditions, is summarised in Table 1. Studies utilising screening tools demonstrated conflicting findings. Initial uncontrolled studies suggested that gender variance based on the parent-reported Child Behaviour Checklist comprising a single item 110 "wishes to be opposite sex" found that positive responses occurred up to 7–8 times more frequently in individuals with ASD compared

Table 1 Key papers

Study (first author, year)	Design	Groups	Type of measure	Measures	Relevant findings
Prevalence of autism spectrum disorder in individuals with gender dysphoria					
Adults					
Heylens (2018) (Gunter Heylens et al. 2018)	Cross-sectional analysis and retrospective analysis of clinical chart data	Adults with gender dysphoria or GID Cross-sectional analysis n = 63 Clinical chart data n = 532	Formal diagnosis and screening test	Social Responsiveness Scale—Adult version (SRS-A) Autism Quotient (AQ) Chart analysis for prior diagnosis of ASD	27.1% mild-severe social shortcomings 4.8% scored above cut-off for AQ 6% prior diagnosis of ASD
Pasterski (2014) (Pasterski et al. 2014)	Cross-sectional analysis	Adults with gender dysphoria or GID, n = 91	Screening test	AQ	5.5% above cut-off for AQ
Jones (2012) (Jones et al. 2012)	Cross-sectional analysis	Transgender adults: Trans men n = 61 Trans women n = 198 Typical adults n = 174 Adults with Asperger syndrome n = 125	Screening test	AQ	30% Medium or narrow autism phenotype in sample of trans men
Kristensen (2015) (Kristensen and Broome 2015)	Cross-sectional analysis	Adults with gender dysphoria n = 446	Formal diagnosis and screening test	Past diagnosis of ASC AQ-10	13% had a past diagnosis of ASC 39% of cohort scored ≥ 6/10 on the AQ
Fielding (2018) (Fielding and Bass 2018)	Retrospective case-cohort study	Adults referred to a gender clinic n = 153	Formal diagnosis	Question regarding previous formal diagnosis	7.8% reported past diagnosis of ASD
Mermaat (2018) (Vermaat et al. 2018)	Cross-sectional analysis	Adults referred to clinic for gender dysphoria n = 326 Typically developing adults n = 1316	Screening test	AQ	No difference in AQ between gender dysphoric and typically developing populations
Stagg (2019) (Stagg and Vincent 2019)	Cross-sectional analysis	Trans or non-binary adults n = 109 Cisgender adults n = 68	Formal diagnosis and screening	Past diagnosis of ASC	14% of transgender or nonbinary participants had past diagnosis of ASC, cf. 4% cisgender participants
Nobili (2018) (Nobili et al. 2018)	Cross-sectional analysis	Transgender adults n = 656 Matched cisgender controls n = 656	Screening test	AQ short	45% of participants 'assigned female at birth' in the transgender group scored above the cut-off of ≥ 70, cf. 30% of AFAB in the cisgender group
Children and adolescent cohorts					
de Vries (2010) (de Vries et al. 2010)	Cross-sectional analysis	Children and adolescents referred to a gender clinic n = 204	Formal diagnosis	Diagnostic Interview for Social and Communication Disorders 10th revision (DISCO-10)	7.8% ASD

Table 1 (continued)

Study (first author, year)	Design	Groups	Type of measure	Measures	Relevant findings
Shumer (2016) (Shumer et al. 2016)	Retrospective cross-sectional analysis of clinical chart data	Youth aged 8-20 years old presenting to a gender clinic n = 39	Screening test	Review of charts for past application of Asperger Syndrome Diagnostic Scale (ASDS) a screening tool for ASD.	23.1% possible (n = 1), likely (n = 6) or very likely (n = 2) Asperger Syndrome
Skagerberg (2015) (Skagerberg et al. 2015)	Cross-sectional analysis and retrospective analysis of clinical chart data	Young people with gender dysphoria attending a gender clinic n = 166	Screening test	SRS	54.2% in mild/moderate or severe range for social shortcomings
VanderLaan (2015)—1 (VanderLaan et al. 2015)	Cross-sectional analysis	Children with gender dysphoria, n = 49	Screening test	SRS	44.9% in clinical range for autism
VanderLaan (2015)—2 (VanderLaan et al. 2015)	Cross-sectional analysis	Children referred to a gender clinic n = 534 Gender-clinic referred children's siblings n = 419 Clinic-referred and non-clinic referred children n = 1201	Screening test	Teacher's Report Form items 9 and 66	Item 9 elevated compared to participants' siblings Item 66 elevated compared to non-referred children, not compared to clinic-referred children
Zucker (2017) (Zucker et al. 2017)	Cross-sectional analysis and cross-validation study with VanderLaan (2015a, b)—2	Children referred to a gender clinic n = 386 Children referred to psychiatric clinic n = 965 Non-referred children n = 965	Screening test	Teacher's Report Form items 9 and 66, assessing obsessional interests and compulsions	Item 9 significantly endorsed compared to control and psych-referred samples Item 66 elevated compared to control, but not relative to children referred to psychiatric facilities
Akgul (2018) (Akgul et al. 2018)	Cross-sectional analysis	Children and adolescents with gender dysphoria n = 25 Typically-developing (TD) children and adolescents n = 50	Screening test	Social Responsiveness Scale (SRS) Behaviour Rating Inventory of Executive Function	68% in mild-severe range for social shortcomings in transgender sample Significantly higher BRIEF global scores compared to control group
Van der Miesen (2017) (van der Miesen et al. 2017)	Cross-sectional analysis	Children with gender dysphoria n = 490 Children with ASD n = 196 TD children n = 2507	Screening test	Children's Social Behaviour Questionnaire	Higher rates of autistic traits on all domains for children with gender dysphoria compared to TD children
Nahata et al. (2017) (Nahata et al. 2017)	Retrospective cross-sectional analysis of clinical chart data	Children and adolescents identifying as transgender (n = 79)	Formal diagnosis	Review of clinical chart data for previous diagnosis of ASD	Previous diagnosis of ASD in 5% of the sample
Leef (2019) (Leef et al. 2019)	Cross-sectional analysis	Children referred for gender dysphoria n = 61 Children referred for other clinical concerns n = 40	Formal diagnosis	Medical record review	Of the children referred for gender dysphoria, 21.3% had a former clinical diagnosis of ASD

Table 1 (continued)

Study (first author, year)	Design	Groups	Type of measure	Measures	Relevant findings
Prevalence of ADHD and gender dysphoria					
Holt (2016) (Holt et al. 2016)	Retrospective cross-sectional analysis of clinical chart data	Children and adolescents referred to a gender clinic n = 218	Formal diagnosis	Review of clinical chart data, referral letters and reports for past diagnosis of Autism Spectrum Conditions (ASC) and/or ADHD	ASC present in 13.3% ADHD present in 8.3%
Dawson (2017) (Dawson et al. 2017)	Cross-sectional analysis	Adults identifying as transgender, n = 54 Total sample n = 6727	Formal diagnosis	Question relating to history of diagnosis of ADHD	Past diagnosis of ADHD in 20.4% of participants
Kaltiala-Heino (2015) (Kaltiala-Heino et al. 2015)	Retrospective cross-sectional analysis and qualitative analysis of clinical chart data	Adolescents attending an adolescent gender identity service for sex reassignment therapy n = 47	Formal diagnosis	Review of participant clinical data for past diagnosis of ASD or ADHD	ASD had been diagnosed in 26% of participants ADHD had been diagnosed in 11% of participants
Cheung (2018) (Cheung et al. 2018)	Cross-sectional analysis	Transgender adults n = 540	Formal diagnosis	Review of electronic medical records	4.8% had past diagnosis of ASC 4.3% had past diagnosis of ADHD
Gender dysphoria in cohorts with diagnosed ASD or ADHD					
Strang (2014) (Strang et al. 2014)	Retrospective cross-sectional analysis of clinical chart data	Children referred with: ASD n = 147 ADHD n = 126 Medical neurodevelopmental disorder n = 116 Control sample n = 165 Non-referred children from CBCL sample n = 1605	Screening test	Child Behaviour Checklist (CBCL) item 110: "Wishes to be opposite sex" to assess gender variance	Participants with ASD were 7.59 times more likely to express gender variance than the non-referred group. Participants with ADHD were 6.64 times more likely to express gender variance than the non-referred group.
George (2017) (George and Stokes 2017)	Cross-sectional analysis	Adults with ASD n = 310 TD individuals n = 261	Screening test	Gender-Identity/Gender-Dysphoria Questionnaire	Rates of gender dysphoria significantly higher in individuals with ASD
May (2017) (May et al. 2017)	Cross-sectional analysis	Children and adolescents with ASD n = 176 Children referred to psychiatric clinics n = 1605 Non-referred children n = 1605	Screening test	Child Behaviour Checklist item 110	4.0% of participants with ASD had gender variance, similar to the referred group

Table 1 (continued)

Study (first author, year)	Design	Groups	Type of measure	Measures	Relevant findings
Janssen (2016) (Janssen et al. 2016)	Retrospective cross-sectional analysis of clinical chart data	Children and adolescents with ASD n = 492 Non-referred children and adolescents n = 1605	Screening test	Child Behaviour Checklist item 110	Participants with ASD were 7.76 times more likely to report gender variance
Dewinter et al. (2017)	Cross-sectional analysis	Adolescents and adults with ASD (n = 675) Control (n = 8064)	Screening test	Questions relating to gender identity	<1% of individuals in the ASD group identified as the sex opposite to that assigned to them at birth 22% of women and 8% of men in the ASD group reported gender non-conforming feelings
Van der Miesen (2018) (van der Miesen et al. 2018b)	Cross-sectional analysis	Adolescents (n = 573) and adults (n = 807) with ASD Adolescents (n = 1016) and adults (n = 846) from the general population	Screening test	Youth Self-Report (item 110 – Wish to be of opposite gender) Adult Self-Report (item 110 as above)	6.5% of adolescents with ASD endorsed item 110 cf. 3.1% of controls 11.4% of adults with ASD endorsed item 110, cf. 5.0% of controls
Walsh (2018) (Walsh et al. 2018)	Cross-sectional analysis	Adults and children with autism n = 669	Formal diagnosis and screening test	Gender identity question	15% of participants self-identified as trans or non-binary
Hisle-Gorman (2019) (Hisle-Gorman et al. 2019)	Retrospective case-cohort study	Children with ASD n = 48,762 Children without ASD n = 243,810	Formal diagnosis	ICD-9 criteria for ASD, GD and related conditions	Children with ASD were over four times as likely to be diagnosed with a condition indicating gender dysphoria

to the general population (Janssen et al. 2016; Strang et al. 2014). However, when compared to children and adolescents referred to clinical services for other mental health concerns, there was no difference in positive responses to item 110 (May et al. 2017). The most definitive findings come from a recent large retrospective case-controlled study of 48,762 children with previously diagnosed ASD matched to 243,810 children without ASD. Based on ICD-9 diagnostic criteria, children with ASD were over four times as likely to be diagnosed with GD (Hisle-Gorman et al. 2019).

Discussion

This is the first systematic review assessing the prevalence of ASD and ADHD in transgender individuals and it demonstrates a paucity of data. The few studies employing diagnostic criteria for ASD suggest a prevalence of 6–26% in people with GD but there are no adequately controlled studies. There are a lack of studies examining prevalence of ADHD. Prevalence of autistic traits identified on screening tools are significantly overestimated amongst transgender populations and unreliable. Further population-based and controlled studies using diagnostic criteria for ASD and ADHD are required.

Prevalence of Autism Spectrum Disorder in Individuals with GD

Whilst many clinicians argue that there is a clear increased prevalence of ASD amongst people with GD, to-date, this has not been based on robust evidence, with existing studies utilising screening tools, self-report, retrospective chart review, and importantly, a lack of control groups (Turban and van Schalkwyk 2018a). The international gold standard for diagnosis of ASD, in contrast, specifies application of diagnostic criteria and rigorous examination including parental interview with developmental history, child observation, and thorough physical examination including hearing assessment (Taylor et al. 2016), hence the findings of studies using ASD screening tools must be viewed with caution.

Adult Cohorts

Of the 21 papers reviewed, seven studies utilised a diagnostic measure (clinical chart review for past diagnoses of ASD) and amongst adults with gender dysphoria found ASD prevalence rates of 4.8–13% (Cheung et al. 2018; Fielding and Bass 2018; Gunter Heylens et al. 2018; Holt et al. 2016; Kaltiala-Heino et al. 2015; Kristensen and Broome 2015; Stagg and Vincent 2019).

Many more studies however, utilised a popular screening test for ASD, the Autism Quotient (AQ), a 50-question self-reported measure (Booth et al. 2013; Kristensen and Broome 2015). The AQ was most commonly analysed as a dichotomous scoring system, where a grade of 32 or higher classified an individual as having autistic traits, providing sensitivity and specificity of 76.71% and 74.07%, respectively (Woodbury-Smith et al. 2005). Based on this cut-off, the prevalence of autistic traits in three studies ranged from 2.1 to 5.5% in people with GD (Gunter Heylens et al. 2018; Pasterski et al. 2014; Vermaat et al. 2018). Findings are certainly not consistent with a recent cross-sectional analysis of 109 trans or non-binary adults which found that 28% surpassed the AQ cut-off of > 32 (Stagg and Vincent 2019), yet other cross-sectional analyses have found no significant difference in AQ results in adults referred to a clinic for GD compared with typically developing adults (Nobili et al. 2018; Vermaat et al. 2018). This clearly highlights significant limitations and lack of utility in the use of AQ as a screening tool amongst people with GD.

These disparate prevalence rates confirm that results depend very much upon methodology and test sensitivity and specificity. The absolute reliability of prevalence rates established from such screening tests is far from conclusive however most tend to suggest a likely higher prevalence of ASD amongst individuals with GD. It is also worth noting that most of the earlier published literature associating ASD and GD takes the form of case reports, in which no inference regarding prevalence can be made (Kraemer et al. 2005; Landen and Rasmussen 1997; Lemaire et al. 2014; Tateno et al. 2015; Williams et al. 1996).

Children and Adolescent Cohorts

Data relating to children and adolescents is more abundant than that available for adults. Three studies conducted medical record reviews to examine past diagnosis of ASD in their cohorts, with variable results ranging from 5 to 26% of children and adolescents referred to a gender clinic (Kaltiala-Heino et al. 2015; Leef et al. 2019; Nahata et al. 2017). The most reliable study used clinical assessment and the Diagnostic Interview for Social and Communication Disorders version 10 (DISCO-10) to identify diagnoses of ASD in 204 children and adolescents referred to a gender clinic in the Netherlands (de Vries et al. 2010). Notably, not all children referred to gender clinics are diagnosed with GD and a confirmed diagnosis of GD was made in 63.2%. Of these confirmed cases, 4.7% were diagnosed with concurrent ASD, 26% were diagnosed with 'subthreshold GD not otherwise specified', and 17.0% were diagnosed with ASD alone. The overall incidence of ASD in this sample was 7.8% and is likely a better representation of the true prevalence compared to medical record reviews. No diagnoses of ASD were made in the cisgender children who comprised 10.8% of those referred to the clinic. This study highlights

considerable overlap between symptoms of ASD and symptoms of gender variance, exemplified by the subthreshold group which may display symptoms which could be interpreted as either ASD or gender variance.

Overlap between symptoms of ASD and symptoms of GD may well confound results. The majority of evidence available for review here is based on cross-sectional studies employing screening tools which lack specificity and are not validated for diagnosis of ASD without additional clinical evaluation. A study by Shumer et al. (2016) found that 23.1% of their cohort of children and adolescents referred to a gender clinic had possible, likely or very likely Asperger Syndrome, based on a parent-completed Asperger Syndrome Diagnostic Scale (ASDS), but they also acknowledged that several questions on the ASDS they utilised to assess ASD symptoms may be confounded by symptoms of GD (Shumer et al. 2016).

It is even less clear when indirect symptoms of autism, such as social skills, cognitive function and obsessional interests are used as screening tools (Skagerberg et al. 2015; VanderLaan et al. 2015a, b; Zucker et al. 2017). The Social Responsiveness Scale (SRS), a screening tool originally used to measure communication and social skill deficits in children, suggests that 45% to 68% of young people with GD have autistic symptoms based on criteria including 'has difficulty relating to peers' (Akgul et al. 2018; Skagerberg et al. 2015; VanderLaan et al. 2015). The SRS has not been validated for use in those with GD and, as deficits in social reciprocity and communication occur in depression and GD (i.e. due to fear of stigma or discrimination), it lacks sensitivity (Moul et al. 2015; Pine et al. 2008; Turban 2018). Executive function tasks, such as planning, decision-making, and memory, which can be compromised in people with ASD, are also not assessed with the SRS (Leung et al. 2016). Akgul et al. (2018) examined both social skills and an indirect measure of executive function using the SRS and the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire respectively (Akgul et al. 2018). Whilst lower executive function in children with GD compared to matched controls was found, given the limitations of the tools, inferences are limited and comprehensive clinical assessment would be more useful.

In addition to compromised social skills and executive function, autism associated obsessional interests may potentially result in a misdiagnosis of autism if an individual demonstrates a strong interest in gendered items associated with the opposite sex (Parkinson 2016; Tateno et al. 2008; Williams et al. 1996). Two studies employed two items from the Child Behavior Checklist (CBCL), a well-validated parent-report questionnaire of behaviour problems designed to assess obsessions (for example, Item 9: 'Can't get his/her mind over certain thoughts') and compulsions (for example, Item 66: 'Repeats certain acts over and over') in children referred to gender clinics. The studies observed that while obsessional interests were certainly higher in children referred to gender clinics compared to a control population, notably, increased levels of compulsions were evident in both children referred to gender clinics and children referred for psychiatric services in general (VanderLaan et al. 2015; Zucker et al. 2017). There is likely an over-representation of autistic symptoms in children and adolescents with GD when compared with healthy control populations (van der Miesen et al. 2017) highlighting limited utility of using such tools to assess ASD in people with gender variance. Furthermore, there may have been a selection bias in previous studies assessing individuals attending gender clinics. Not only may individuals who attend clinics not necessarily have GD, individuals who do have impaired social functioning may be unable to communicate their feelings of GD effectively enough to seek treatment. Further studies utilising diagnostic criteria on differentiating low functioning and high functioning autism in the population with GD are needed.

Prevalence of ADHD and GD

Four studies—two in adult cohorts, and two in paediatric cohorts—suggest a higher prevalence of ADHD amongst people with GD (Cheung et al. 2018; Dawson et al. 2017; Holt et al. 2016; Kaltiala-Heino et al. 2015). A retrospective chart review of a UK paediatric gender clinic found a prevalence of ASD in 13.3% and ADHD in 8.3% of their cohort, both at least five times that of UK general population rates, while a similar study in Finland reported prevalence of 26% and 11% for ASD and ADHD respectively (Holt et al. 2016; Kaltiala-Heino et al. 2015; Russell et al. 2014). Co-occurrence of ASD and ADHD was not reported in either study. In the adult literature, a convenience sample from a paid online survey found that of 6727 participants, 54 identified as transgender, with 20.4% of these 54 individuals receiving a previous diagnosis of ADHD (Dawson et al. 2017). Notably, there were multiple limitations: self-reported diagnoses, a bias towards young internet users, and, as birth-assigned sex was not asked, the sample captured is unlikely to be representative of transgender cohorts (Dawson et al. 2017). A recent Australian study in 540 transgender adults reported past diagnosis of ADHD in 4.3% of participants, and was limited by similar issues (Cheung et al. 2018). Potentially, misdiagnoses of ADHD may also be a contributing factor to high rates of ADHD in this sample. Gender non-conforming youth often present with externalising behaviours (Coleman et al. 2012) and symptoms such as attention deficit, impulsivity, and hyperactivity may be explained in part by ASD rather than ADHD, even though distinguishing the two diagnoses is usually achievable (Dickerson Mayes et al. 2012). While there may be some overlap in symptoms of GD, ASD and ADHD, the rates of ADHD in both paediatric and adult

populations was found to be elevated relative to the general population, hence further research is warranted to establish the true rates of these conditions in transgender individuals.

GD in Cohorts with Suspected or Confirmed ASD or ADHD

When examining autistic traits in individuals with GD, a small number studied the reverse—prevalence of GD or gender variance in individuals with ASD (Dewinter et al. 2017; George and Stokes 2017; Hisle-Gorman et al. 2019; Janssen et al. 2016; May et al. 2017; Strang et al. 2014; van der Miesen et al. 2018b; Walsh et al. 2018). Recently, the largest controlled study involving over 48,000 children with ASD, each matched to five controls, found that children with ASD were over four times as likely to be diagnosed with a condition indicating GD as per the ICD-9, illustrating a clear overrepresentation of GD in the ASD population (Hisle-Gorman et al. 2019). This is the most compelling evidence to date that there is a higher prevalence of GD in those with ASD.

Conclusions

Though evidence suggesting that ASD and ADHD are more prevalent in the transgender community exists, it is of low quality. Retrospective clinical chart reviews assessing formal diagnoses of ASD or ADHD represent the best evidence, but no adequately controlled studies utilise diagnostic criteria. Screening tests cannot be reliably used to determine prevalence of ASD or ADHD. With some overlapping symptoms, the potential for misdiagnosis is possible and any diagnostic tests for ASD and ADHD will need to be validated for use in the transgender population. From a practical clinical perspective for individuals who do have concurrent GD and ASD, guidelines have recently been published highlighting a need for potential extended assessment and decision-making periods (Strang et al. 2018). Most importantly, a diagnosis of ASD should not exclude people from gender-related medical supports. People with neurodevelopmental conditions and GD should be supported in the strengths of neurodiversity and gender diversity and reassured that these conditions do not preclude any forms of affirmative clinical care (Turban and van Schalkwyk 2018b). Further rigorously-designed research examining the prevalence of these conditions amongst people with GD is required to correct the dearth of literature on the topic. Until then, individualised treatment and design of health care services for transgender individuals should consider assessment for, and management of, both ASD and ADHD in their protocols for gender-affirming care.

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Compliance with Ethical Standards

Conflict of interest The authors have nothing to declare.

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Youths with a non-binary gender identity: a review of their sociodemographic and clinical profile

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Many of the considerable number of young people who identify as transgender or gender diverse do not conform to traditional binary notions of gender (male *vs* female), and instead have a non-binary gender identity. This narrative Review summarises literature related to the sociodemographic and clinical profiles of young people with a non-binary gender identity. Young people identifying as non-binary form a substantial minority of the general population. They experience lower levels of support and are at increased risk of experiencing abuse and victimisation than young people who are cisgender. Furthermore, compared with young people who are transgender and binary, people who identify as non-binary experience less access to trans-specific health care. Young people identifying as non-binary have poor mental health outcomes, with high rates of depression, anxiety, and suicidal ideation that were found to be similar if not higher than in those who are transgender and binary. This Review highlights that young people who identify as non-binary are highly vulnerable and likely to have important health-care needs.

Introduction

There is growing research interest in young people (aged ≤25 years) identifying as transgender and gender diverse, which is defined as having a gender identity that differs from a person's birth-assigned sex.[1] Although most youths who are transgender and gender diverse identify their gender in a binary way (ie, as either male or female, which is often connected to the descriptors of having a transmasculine or transfeminine identity), a considerable proportion have a gender identity that falls outside of a male or female gender binary. Non-binary has therefore emerged as an umbrella term[2,3] that is used to describe a variety of gender identities that are outside of the binary.[2,4–7] This Review incorporates under the non-binary label many of these identities—including genderqueer, genderless, gender-neutral, trigender, agender, third gender, two-spirit, and bigender. It is important to note that some youths with a non-binary gender identity do not identify as transgender at all,[3] and this Review uses the term non-binary gender identity regardless of whether such an individual identifies as transgender and gender diverse.

There is a dearth of research focusing on the existence and experience of individuals who do not have a traditional, binary gender identity.[2,8,9] For example, most studies characterising the clinical outcomes of people who are transgender focus primarily on the use of gender-affirming hormones by those with binary gender identities; such affirming interventions might not be as sought after by individuals with non-binary identities, because they might not want to acquire either female or male sexual characteristics.[2] However, it is still important to ensure that people with non-binary identities have similar access as others to such gender-affirming hormones.[10] There are also concerns regarding the vulnerability of people with non-binary identities because of their divergence from societal norms.[2,3] In particular, these individuals face unique difficulties in gender-segregated scenarios, such as choosing a title to use on official documentation or deciding which gendered toilet to use.[2,4,11–13]

Most studies on the non-binary population, although few in number, have focused on adults, with one population-based study in Belgium reporting that 2·2% (95% CI 1·5–3·4) of adults who were assigned male at birth and 1·9% (1·0–2·8) of adults who were assigned female at birth have a non-binary identity.[14] Others have profiled the nature of transition, namely the process of changing appearance, pronoun, or names to be more consistent with a person's gender identity. Multiple studies have observed that people with a non-binary identity are less likely to have transitioned socially or medically (eg, through hormonal treatments) than are those with a binary identity.[15,16] Finally, some studies have reported that adults with a non-binary identity have greater barriers to care and worse mental health outcomes than do the binary transgender population.[17,18] This difference is often explained by the minority stress model,[19–21] in which poorer mental and physical health outcomes are frequently found in members of a minority group because of the stigma, prejudice, and increased stress that they face.

Currently, about 11·0–14·7% of the transgender and gender diverse youth population seeking specialist gender-affirming care have a non-binary identity.[4,22] This number is likely to increase substantially, considering the increased awareness of gender variance in modern society and the substantial increase in referrals to gender clinics worldwide.[23–25] However, as already mentioned, knowledge regarding young people who identify as non-binary is distinctly scarce. Thus, the aim of this Review is to synthesise and appraise current literature on children and adolescents with non-binary gender identities, so that clinicians working with this population have ready access to the relevant literature. We first describe sociodemographic and epidemiological characteristics, including prevalence, age and birth-assigned sex differences, and social supports. Next, we review relevant clinical data, including access to care and use of hormonal interventions, and we describe the psychological characteristics of young people with non-binary identities. Finally, we highlight important gaps in knowledge and discuss

potential future directions, with the ultimate aim that this Review will help improve health-care services for young people with non-binary identities and help guide future research.

We included in this Review studies whose participants were younger than 25 years and were described as having a gender that did not fall exclusively within the binary norms of male and female.[4–7,22,26–40] Within the studies included (table), several used the same dataset for their analyses, specifically a group of transfemales in the San Francisco Bay Area,[5,33] the Canadian Trans Youth Health Survey,[29,36,38,40] and young people who are transgender attending the UK National Gender Identity Development Service.[4,22]

Epidemiological and sociodemographic and information

Gender identity descriptors

Many different descriptors are used by young people to self-refer to a gender identity that lies outside of the male–female binary. It is important for clinicians and researchers to be aware of this large diversity in terminology, to ensure that they use the correct descriptors in health-care or research settings when working with this population. Several studies have compared the frequency of such descriptors. In general, the terms genderqueer (ranging from 9·7% to 61·5%) and genderfluid (18·5–35·4%) were the most popular descriptors among study populations, and other terms, such as non-binary (7·7–18·5%), other gender identity (12·8–21%) and agender (1·2–17·9%), were less commonly used.[6,22,31,36]

This varying use of gender identity descriptors is likely to be the result of the different methodologies used to capture information about gender identity. In particular, a study[31] that determined that 24 (61·5%) of 39 people with non-binary identities have a genderqueer identity provided only two non-binary options—genderqueer and other—to a question about their gender identity, which probably explains the high proportion. In contrast, other studies allowed young people with non-binary identities to fill in a free-text box, inviting them to describe their gender identity themselves.[6,22,36]

Prevalence

In most studies, young people were identified as being non-binary if their gender identity was outside of the traditional male–female dichotomy (ie, a combination of male and female, or neither male nor female). This definition will be used in what follows unless otherwise stated. Two large, population-based studies reported a similar prevalence of young people with non-binary identities.[6,26] In one of these studies,[6] 350 (1·8%) of 19 385 US high-school students aged 13–19 years self-reported a non-binary gender identity, defined as being different to male or female, or transmale or transfemale identities. In the second study,[26] 12 (1%) of 1195 individuals aged 12–24 years from rural and remote areas of Scotland identified as non-binary. However, two other studies reported a considerably higher prevalence.[27,35] The first of these studies[27] had a relatively small sample size and reported that 10% of 230 US high-school students and (8%) of 61 US middle-school students had a non-binary identity. In this study, a wider definition of non-binary identity was used, which also included people who identified as lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ), so the reported prevalence is probably an overestimate.[27] The second study,[35] an online community survey of 782 people from Spain aged 14–25 years, found a similarly high prevalence (70 [9%]) of people with non-binary identities. However, the comparatively high prevalence in this study could also be misleading, because participants were recruited through LGBTQ organisations, which might have resulted in a higher proportion of people who are transgender and gender diverse than in the general population.[35]

Many studies have focused on determining the number of children and adolescents who have a non-binary gender identity in specific populations, and the results vary greatly. Two studies[4,22] found a relatively low prevalence (between 11% and 14·7%) of young people with non-binary identities in the transgender and gender diverse population who were attending the UK National Gender Identity Development Service, a specialist gender clinic. This low number, compared with that of the other groups we describe, could be an underestimate because young people might be reluctant to reveal a non-binary identity in a clinical setting owing to fears regarding how medical professionals might react.[22] In contrast, the largest proportions (41–66%) of young people with non-binary identities were found in online surveys of young people who already identify as transgender from the UK, Australia, and Canada.[7,28,29] All of these studies used non-random sampling, and participants were either recruited through online means (eg, Facebook) or community organisations. Two studies from the USA,[5,33] focusing specifically on individuals who already identify as transgender and were assigned male at birth, determined that only 18·8–22·3% of these individuals had a non-binary identity. Adolescents who are sexual and gender minorities (LGBTQ) from the USA were also surveyed, 20·5–22·3% of whom identified as genderqueer.[30,31] Another study[32] examined the same US subgroup and reported that a substantially higher proportion (57·7%) were gender non-conforming (ie, without an exclusive male or female identity), but the authors of this study specifically focused on participants who were romantically or sexually interested in cisgender individuals (ie, people whose gender identity is the same as their birth-assigned sex).

In summary, there is considerable variability in prevalence rates of young people who identify as non-binary, which appear to be influenced by the specific

	Study type	Location	Sample (n) and groups	Population	Age (years)	Types of measure(s)			Variables
						Socio-demographic	Clinical	Psycho-logical	
Aparicio-García et al (2018)[35]	Cross-sectional survey	Spain	782 people who are cisgender (532), transgender (180), or non-binary (70)	People recruited through websites, Twitter, and different associations	14–25	✓	..	✓	Prevalence (self-reported), religion, social supports, sexual orientation, life satisfaction, abuse and victimisation, alcohol, smoking, drug use, and suicidal thoughts (all survey questions), and overall mental health (General Health Questionnaire; GHQ-12)
Arayasirikul et al (2016)[5]	Prospective, longitudinal survey	USA	300 transfemales	San Francisco Bay Area population,* recruited through peers and online	16–24	✓	..	..	Prevalence (self-reported)
Bosse and Chiodo (2016)[31]	Cross-sectional survey	USA	175 people who are AFAB (136) or AMAB (39)	People who are LGBTQ, recruited through local youth-serving organisations and Facebook groups	18–25	✓	..	..	Prevalence and birth-assigned sex (self-reported), gender identity descriptors (multiple choice), and sexual orientation (multiple choice)
Carrillo et al (2018)[27]	Cross-sectional survey	USA	291 students at middle school (61) or high school (230)	Students in Fresno, California	Not known	✓	..	..	Prevalence (self-reported)
Castillo et al (2016)[36]	Cross-sectional survey	Canada	923 people (various groups)	Canadian Trans Youth Health Survey,* recruited through various methods	14–25	✓	..	..	Gender identity descriptors (survey question and multiple choice)
Chen et al (2018)[32]	Cross-sectional survey	USA	156 people who are cisgender males (3), cisgender female (1), transmales (54), transfemales (8), or non-binary (90)[5]	Sexual and gender minority adolescents who are romantically or sexually interested in cisgender males, recruited through Facebook adverts	14–17	✓	..	..	Prevalence (self-reported) and fertility considerations (15 items: 13 closed-ended and two open-ended survey questions; data not presented)
Clark et al (2018)[29]	Cross-sectional survey	Canada	843 people who are non-binary (344), transmales (356), or transfemales (139), or who were not categorised (4)	Canadian Trans Youth Health Survey,* recruited through various methods	14–25	✓	✓	✓	Prevalence, ethnicity, age, and birth-assigned sex(all self-reported), access and barriers to health care, hormone therapy, overall mental health, alcohol, smoking, drug use, and self-harm (all multiple choice)
Eisenberg et al (2017)[34]	Cross-sectional survey	USA	66 people (in unknown groups)	Sexual and gender minority adolescents from British Columbia, Minnesota, and Massachusetts, recruited through community organisations	14–19	✓	..	..	Sexual orientation
Hughes et al (2017)[26]	Cross-sectional survey	Scotland	1195 people who are cisgender female (590), cisgender male (515), non-binary (12), transgender (8), or did not disclose their gender (70)	Recruited online and through schools, youth groups, and sexual health clinics	12–24	✓	..	..	Prevalence (self-reported)
Johns et al (2017)[33]	Cross-sectional survey	USA	250 transfemales	San Francisco Bay Area population,* recruited through peers and online	16–24	✓	✓	..	Prevalence (self-reported) and access and barriers to health care (survey question)
Johnson et al (2019)[39]	Qualitative interviews	USA	14 people who identify as non-binary	Adolescents living in New York and San Francisco Bay Area	16–20	..	..	✓	Abuse and victimisation (open-ended interview questions)
Jones and Hillier (2013)[28]	Cross-sectional survey	Australia	91 people who identify as genderqueer (43), transmales (21), transfemales (18), or other gender (9)	Trans-spectrum people, recruited online and through media sources, advertisements, and service providers	14–21	✓	..	..	Prevalence (self-reported)

(Table continues on next page)

	Study type	Location	Sample (n) and groups	Population	Age (years)	Types of measure(s)			Variables
						Socio-demographic	Clinical	Psychological	
(Continued from previous page)									
Kaltiala-Heino and Lindberg (2019)[37]	Cross-sectional survey	Finland	133 774 people who are AMAB (65 829) or AFAB (67 945)	Adolescents who completed School Health Promotion Study by the National Institute for Health and Welfare, recruited through schools	<21	✓	..	..	Age and birth-assigned sex (self-reported)
Rimes et al (2017)[7]	Cross-sectional survey	UK	677 people who are transfemales (105), transmales (210), non-binary AMAB (93), or non-binary AFAB (269)	LGBTQ people, recruited through LGBTQ youth organisations, social media, advertisements, and snowball sampling	16–25	✓	..	✓	Age, social class, educational qualifications, ethnicity, sexual orientation, smoking and drug use, mental health and help-seeking, self-harm, and abuse and victimisation (all self-reported), alcohol consumption (AUDIT-C questionnaire), life satisfaction (Satisfaction with Life Scale), and suicidality (revised Suicide Behaviours Questionnaire)
Sterzing et al (2017)[30]	Retrospective cross-sectional survey	USA	1177 people who are cisgender males (389), cisgender females (478), transmales (47), transfemales (19), non-binary AMAB (52), non-binary AFAB (189), or did not answer the question of gender identity (3)	Sexual and gender minority people, recruited online from Facebook adverts and community organisations	14–19	✓	..	✓	Prevalence (self-reported) and victimisation, including sexual abuse (modified Abbreviated Juvenile Victimisation Questionnaire and Swearer Bullying Survey)
Thorne et al (2018)[4]	Prospective, longitudinal study (with use of cross-sectional data)	UK	388 people who are transgender and binary (331) or non-binary (57)	National Gender Identity Development Service,* recruited through the clinic	16–25	✓	..	✓	Prevalence, age, and birth-assigned sex (self-reported), social supports (multidimensional scale of perceived social support), anxiety and depression (hospital anxiety and depression scale), self-esteem (Rosenberg self-esteem scale), and self-harm (Non-Suicidal Self-Injury Questionnaire)
Twist and de Graaf (2018)[22]	Cross-sectional survey	UK	251 people identifying as transgender (140), binary (72), non-binary (30), or undefined (4), or who did not answer (5)	Adolescents attending National Gender Identity Development Service* between June, 2016, and February, 2017	12–18	✓	..	..	Prevalence, birth-assigned sex, age (all self-reported), and gender identity descriptors (Gender Diversity Questionnaire)
Veale et al (2017)[38]	Cross-sectional survey	Canada	923 people (323 aged 14–18 years, 600 aged 19–25 years)	Canadian Trans Youth Health Survey*	14–25	..	..	✓	Overall mental health (4-point scale), levels of stress and hopelessness (ten-item Kessler Psychological scale), and self-harm (multiple choice and survey question)
Watson et al (2017)[40]	Cross-sectional survey	Canada	923 people (323 aged 14–18 years, 600 aged 19–25 years)	Canadian Trans Youth Health Survey*	14–25	..	..	✓	Disordered eating
White et al (2018)[6]	Cross-sectional survey	USA	19 644 people who identified as cisgender females (12 818), cisgender males (6273), non-binary (350), transmales (132), or transfemales (71)	High school students, recruited through schools and social media outlets	13–19	✓	..	..	Prevalence (self-reported), and gender identity descriptors (open-ended response box)

Cisgender refers to people who have a gender identity that is the same as their birth-assigned sex. AFAB=assigned female at birth. AMAB=assigned male at birth. LGBTQ=lesbian, gay, bisexual, transgender, and queer or questioning. *The survey population was the same for various studies that used the data from the Canadian Trans Youth Health Survey,[29,36,38,40] the San Fransisco Bay Area,[5,33] and the UK Gender Identity Development Service.[4,22]

Table: **Main characteristics of the studies included**

subgroups examined rather than by geographical location. Existing studies suggest that 1–10% of the overall population and 11–15% of the specialist gender clinic-based population of young people have a non-binary identity, whereas prevalence estimates of non-binary identities in all young people who are transgender are generally much higher (19–66%). Researchers and clinicians need to consider this large variation and use the most appropriate prevalence estimates based on their specific subpopulation.

Age and birth-assigned sex

Two studies found no differences between the age distribution of participants with non-binary versus binary gender identities,[7,29] including one study of 677 LGBTQ young people (aged 16–25 years) from the UK[7] and another study of 839 transgender young people (aged 14–25 years) from Canada.[29] Consistent with this finding, no differences were seen in the distribution of non-binary identities across age for young adolescents aged 12–18 years attending the UK Gender Identity Clinic.[22] However, Thorne and colleagues determined that the non-binary transgender group (mean age 21 years) was significantly older than the binary group (mean age 20 years; p=0·005) in their study of 388 older adolescents (aged 16–25 years).[4] Similarly, a school survey of 135 760 Finnish adolescents younger than 21 years found that birth-assigned males were more likely to identify as non-binary in older age groups, but that birth-assigned females showed the opposite trend.[37]

Most studies found no significant differences between young people with non-binary and binary identities in terms of birth-assigned sex, with both sets of young people presenting a higher ratio of young people assigned female at birth.[4,22,31] However, the study of 839 Canadian transgender young people[29] showed that significantly more non-binary young people (81·6%) were assigned female at birth than were binary transgender young people (69·9%).

The differences in findings related to age and birth-assigned sex distribution are again probably related to recruitment methods. For example, studies that focused solely on treatment-seeking individuals attending a clinical gender service[4,22] yielded different results to surveys that encompassed a wider population that was either recruited online or through community organisations.[7,29,31,37]

Demographics and sexual orientation

Young people who identify as non-binary were found to be similar to transgender young people who identify as binary in terms of social class,[7] educational qualifications,[7] and ethnicity.[7,29] Similar to their cisgender peers, young people who identify as non-binary were most likely to be located in urban areas and be atheist or agnostic,[35] but they were less likely to identify as heterosexual and more likely to describe themselves as asexual, pansexual, or queer.[7,31,35] Conversely, adolescents who described their sexual orientation with self-generated labels were more likely to use non-binary gender identity descriptors, such as genderqueer or genderfluid than were those who used traditional labels.[34]

Social support

Adolescents with non-binary gender identities have been found to be less likely to be involved with the community and have appropriate support than are cisgender and transgender young people with a binary gender identity. For example, a significantly smaller proportion of adolescents who identify as non-binary (19 [27·1%] of 70) played sport in school or outside of it than did adolescents who are cisgender (248 [46·6%] of 532) or binary transgender (89 [49·4%] of 180), and a smaller proportion of people who are non-binary (6 [8·6%] of 70) had a remunerated job than did cisgender (126 [23·7%] of 532) and binary transgender (23 [12·8%] of 180) individuals.[35] Furthermore, adolescents who identify as non-binary were less likely (14 [26·4%] of 53) to have family support than were cisgender (186 [58·7%] 317) or binary transgender (86 [51·2%] of 168) individuals, and adolescents identifying as non-binary were also less likely (25 [42·4%] of 59) to have adult support outside the family than were cisgender (169 [57·9%] of 292) and binary transgender adolescents (98 [58·3%] of 168). Finally, adolescents identifying as non-binary were less likely (54 [84·4%] of 64) to have support from friends than were cisgender (312 [96%] of 325) and binary transgender adolescents (153 [87·9%] of 174).[35]

However, these findings differed from those of another study,[4] which found no differences in the perceived level of support from significant others, family, friends, and among transgender individuals with non-binary and binary identities. This discrepancy might stem from the fact that the second study focused on a population of adolescents receiving clinical services from national specialist gender clinics in the UK, which could be intrinsically biased towards people who receive relatively high levels of support. This bias would, for instance, allow these adolescents more readily to overcome the challenges inherent in obtaining referrals, booking appointments, and attending clinics.[4] Regardless of these conflicting results, transgender individuals with binary identities have been found to have less support than do cisgender individuals,[41,42] making it likely that young people with non-binary identities will also have lower levels of support and be more isolated from the wider community than cisgender individuals. This difference would increase the vulnerability of people identifying as non-binary and make them more susceptible to poorer mental health outcomes, given that social support and connectedness are fundamental protective factors for enhancing resilience in young people.[43,44]

Psychological profile

Abuse and victimisation experiences

Four studies determined that young people with non-binary gender identities experience minority stress in the

form of multiple experiences of abuse and victimisation.[7,30,35,39] Compared with cisgender adolescents, young people with non-binary gender identities had a significantly higher chance of having experienced polyvictimisation (at least ten experiences of victimisation of different types, such as school-based bullying, sexual abuse, or cyberbullying).[30] Furthermore, in a small qualitative study, 14 adolescents identifying as non-binary in the USA were found to have experienced multiple forms of non-affirmation in many different social contexts, such as people not using their preferred pronouns and refusing to accept the existence of non-binary gender identities.[39] Many participants reported that these experiences of invalidation negatively impacted their mood and cognition and ultimately contributed to worsened mental health outcomes.[39]

In terms of specific types of abuse, young people with non-binary identities are at high risk of victimisation. An online survey showed that young people with a non-binary identity had an increased likelihood (29 [42·6%] of 68) compared with cisgender young people (132 [25·2%] of 524) of experiencing verbal abuse at school, as well as out of school (38 [55·9%] of 68 non-binary people *vs* 155 [29·4%] of 527 cisgender people). Young people who identify as non-binary were also more likely (27 [55·1%] of 49) to experience discrimination when looking for a job than were cisgender people (95 [20·6%] of 462).[35] Rates of sexual abuse were also significantly higher in young people with non-binary identities than in cisgender young people (65·4% of people who identify as non-binary and were assigned male at birth; 39·7% of cisgender males; 51·0% of people who identify as non-binary and were assigned female at birth; and 44·8% of cisgender females).[30] Rates of physical attacks at school were elevated for people who are non-binary too (9 [13·6%] of 66 people who identify as non-binary *vs* 43 [8·2%] of 527 cisgender people), as were those of cyberbullying (29 [41·4%] of 70 people who identify as non-binary *vs* 37 [20·9%] of 177 binary transgender people), although these two differences were not statistically significant.[35]

Overall mental health

A large proportion of the published results include a comparison of the mental health of non-binary young people and that of binary transgender young people, and it is important to remember that the latter typically have poor mental health outcomes themselves.[45] Among 843 gender diverse Canadian young people, adolescents with a non-binary identity were more likely to report overall poorer mental health than were binary transgender adolescents,[29,38] as well as higher reported levels of stress and more feelings of hopelessness.[38] In contrast, a study[7] of 677 LGBTQ adolescents reported no differences in mental health between adolescents identifying as non-binary and binary transgender adolescents. This study split adolescents identifying as non-binary into separate groups based on their birth-assigned sex, with 269 who were assigned female at birth and 93 who were assigned male at birth. In a separate study[35] that drew comparisons with both cisgender and transgender young people, adolescents identifying as non-binary reported experiencing significantly more psychological health problems, significantly greater isolation, and significantly less happiness than both groups, which is consistent with the two Canadian studies.[29,38]

Substance use and specific mental health problems

Three studies[7,29,35] compared alcohol consumption, illicit drug use, and smoking among transgender young people with non-binary and binary gender identities, and in each case no statistically significant differences between the two groups were found.

Adolescents identifying as non-binary had significantly higher levels of anxiety and depression and poorer self-esteem than did binary transgender individuals.[4] Among young people identifying as non-binary, people who were assigned male at birth were observed to be less likely to have sought help for depression and anxiety than were people who were assigned female at birth.[7] One study[40] of 923 transgender young people from Canada identified similar rates of disordered eating behaviors in all three groups of young people who were transgender males, transgender females, and non-binary. Binge eating was the most common form of disordered eating (observed in 49 [44·5%] of people aged 14–18 years and 59 [52·7%] of people 19–25 years who are non-binary). Youths identifying as non-binary in the older group were less likely (51 [27·6%]) to lose weight by fasting than were transgender males in the younger age group (64 [34·4%]). However, in the younger age group, youths with a non-binary gender identity had higher rates (28 [25·0%]) of losing weight by vomiting than did transgender males (13 [10·6%]).[40]

Evidence is conflicting regarding the rates of self-harm and suicidal ideation in young people with a non-binary identity compared with transgender and gender diverse individuals with a binary identity. Two studies[29,38] found that adolescents identifying as non-binary reported more self-harm (77% reported self-harm at least once in the past year) than did transfemales (50%) and similar rates to transmales (79·2%). Another study[35] reported that adolescents identifying as non-binary were more likely to have suicidal thoughts than were cisgender people (odds ratio [OR] 4·43) and binary transgender young people (OR 1·57). However, a further study[4] found similar rates of self-harm in both non-binary (35 [61·4%] of 57) and binary groups (193 [58·3%] of 331).

Clinical experiences

Access and barriers to health care

Canadian transgender young people identifying as non-binary have been found to be less likely to have a family doctor and less comfortable speaking with family doctors about their gender identity and associated gender-related

health-care needs than are young people with a binary transgender identity.[29] Consequently, family doctors of adolescents identifying as non-binary were less likely to be aware of their gender identity.[29] Furthermore, although there were no significant differences in the rates of foregone general health care in the younger non-binary population (aged 14–18 years) compared with binary transgender individuals, older adolescents with non-binary identities (aged 19–25 years) were found to have significantly higher rates of not seeking necessary health care in the previous year (58·1% *vs* 40·2%; p<0·01).[29]

A key difference is that when young people identifying as non-binary sought out general physical or mental health care, they encountered fewer overall problems in accessing their required health care than did young people with a binary transgender identity.[33] This difference could be attributed to their flexibility in presenting a specific gender identity to health-care staff to avoid any stigma or discrimination.[33] However, if young people were seeking out trans-specific health care, individuals identifying as non-binary were twice as likely to experience multiple barriers to care than were transgender adolescents with a binary gender identity (OR 2·01; p=0·013).[29] These barriers included a scarcity of health information to help make an informed decision about beginning hormone therapy, difficulty in finding doctors to prescribe hormones, and primary care doctors frequently being unaware of their patient's gender identity.[29]

Search strategy and selection criteria

We identified references from Jan 1, 1946, to Feb 6, 2019, from MEDLINE (Ovid), EMBASE (Ovid), and PsycINFO (Ovid) databases using thesaurus terms and keywords. We searched PubMed and Tandfonline using keywords to retrieve electronic publications and items not indexed in the aforementioned three databases. The main search terms used were as follows: (non-binary or genderqueer or gender-nonconformity or genderfluid or agender or bigender or trigender or gender-neutral or genderless or non-gendered or third-gender) and (adolescen* or pediatric* or paediatric* or youth* or teen or teens or teenage* or child*). We trialed alternative forms of these words, including hyphens (eg, non-binary) or spaces (eg, gender neutral), but they did not affect the search results. Manual searching of the reference lists of relevant retrieved articles did not identify any additional references. We considered studies eligible for inclusion if participants were 25 years or younger and were described as having a gender that did not exclusively fall within the binary norms of male or female, such as non-binary, genderfluid, or genderqueer. Furthermore, we included studies that contained information related to the sociodemographic characteristics, clinical features, or psychological profile of young people with a non-binary identity. This Review included published studies of any design or language, although we excluded conference abstracts or studies that failed to report results at the group level (eg, case studies).

Hormone therapy

Only one study[29] examined the use of hormone therapy in young people with non-binary identities, finding that fewer people with a non-binary gender identity had commenced or were about to begin hormones than had transgender young people with binary identities. This difference was due to a greater proportion of people still deciding about hormone therapy or not wanting to be on hormones at the time of the survey.[29]

Conclusions

The majority of studies on young people with non-binary gender identities have focused on sociodemographic and epidemiological data,[4–7,22,26–37] and have shown that they comprise a substantial minority of the general, transgender and gender diverse, and LGBTQ populations, although there are often large differences in prevalence estimates.[4–6,22,26–33,35]

Although studies on the health of young people with non-binary identities remain scarce, they nonetheless paint an unsettling picture. As previously observed for binary transgender youth,[46,47] young people with non-binary identities were at much greater risk of experiencing abuse and victimisation than were cisgender individuals, with many experiencing covert victimisation and invalidation through non-affirmation of their gender identity.[7,30,35,39] Young people identifying as non-binary also experienced increased marginalisation, were less involved in the community, and were less likely to have appropriate supports than were not only cisgender youth but also their binary transgender peers (who are already known to fare poorly across these domains).[4,35] Moreover, young individuals identifying as non-binary faced considerably more barriers in accessing trans-specific health care, which included a scarcity of relevant health information and difficulties in obtaining hormonal treatment.[29] Consistent with the minority stress model, these experiences are together likely to have contributed substantially to the high rates of depression, anxiety, and suicidal ideation observed in young people identifying as non-binary, which were found to be similar if not higher than those in their binary transgender peers.[4,35]

The findings of this Review are subject to various limitations. Specifically, the number of studies of youths with a non-binary identity limits our findings, particularly because only two studies examined access and barriers to health care for non-binary children and adolescents,[29,33] only one of which described hormone therapy use in this population.[29] Furthermore, many studies had suboptimal methodology. For example, most of the studies examining the psychological profile of young people with non-binary identities[4,7,29,30,35,38,39] used self-reported measures captured in online surveys,[7,29,35,38] and researchers have highlighted

the need for clinical assessments to provide a more thorough understanding of participants' mental health and to confirm the findings of the studies.

This is, to our knowledge, the first narrative Review of the sociodemographic and psychological health characteristics of young people identifying as non-binary. The results of this Review have highlighted that young people identifying as non-binary are highly vulnerable, considering that they have lower levels of support, are at greater risk of experiencing abuse and victimisation, and have poorer mental health outcomes than do cisgender young people. Therefore, future empirical investigation in this area should extend beyond simple socio-demographic data and focus on addressing the important health-related knowledge gaps. On the one hand, studies assessing health professionals' knowledge and understanding of, and comfort in treating young people who identify as non-binary are clearly warranted as a first step to removing barriers to care. On the other hand, improved understanding of the specific health-care requirements of young people identifying as non-binary (which might differ across various domains, including medical and surgical transition, and sexual health needs) and their psychosocial profile would directly assist clinicians to provide better targeted care for this vulnerable and stigmatised population.

Contributors

DC designed the literature review, screened studies for inclusion or exclusion, extracted relevant information from the included articles, drafted the initial manuscript, and revised the manuscript. KCP, MAT, and ZP contributed to the conceptualisation and design of the literature review, and reviewed and revised the manuscript. ASC and SZ reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of interests

We declare no competing interests.

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Position statement on the hormonal management of adult transgender and gender diverse individuals

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Abstract

Introduction: Rising demand for gender-affirming hormone therapy mandates a need for more formalised care of transgender and gender diverse (TGD) individuals in Australia. Estimates suggest that 0.1–2.0% of the population are TGD, yet medical education in transgender health is lacking. We aim to provide general practitioners, physicians and other medical professionals with specific Australian recommendations for the hormonal and related management of adult TGD individuals.

Main recommendations:

- Hormonal therapy is effective at aligning physical characteristics with gender identity and in addition to respectful care, may improve mental health symptoms.
- Masculinising hormone therapy options include transdermal or intramuscular testosterone at standard doses.
- Feminising hormone therapy options include transdermal or oral estradiol. Additional anti-androgen therapy with cyproterone acetate or spironolactone is typically required.
- Treatment should be adjusted to clinical response. For biochemical monitoring, target estradiol and testosterone levels in the reference range of the affirmed gender.
- Monitoring is suggested for adverse effects of hormone therapy.
- Preferred names in use and pronouns should be used during consultations and reflected in medical records.
- While being TGD is not a mental health disorder, individualised mental health support to monitor mood during medical transition is recommended.

Changes in management as result of this position statement: Gender-affirming hormone therapy is effective and, in the short term, relatively safe with appropriate monitoring. Further research is needed to guide clinical care and understand long term effects of hormonal therapies. We provide the first guidelines for medical practitioners to aid the provision of gender-affirming care for Australian adult TGD individuals.

Being transgender or gender diverse (TGD) is now viewed as part of the natural spectrum of human diversity.[1] Estimates suggest that 0.1–2% of the population are TGD.[2] TGD people are individuals whose gender identity is markedly and persistently incongruent with their sex assigned at birth. They often experience intense body dysphoria driving individuals to seek gender-affirming hormone therapy to align physical characteristics with gender identity. Stigma and discrimination contribute to poor mental health. Australian data demonstrate that over 50% have medically diagnosed depression and are at high risk of suicide.[3–5]

The World Health Organization International Classification of Diseases 11th Revision has recently declassified gender incongruence as a mental health disorder, with a goal to decrease stigma and social exclusion.[6] Nonetheless, as those with gender incongruence have specific health needs, an understanding of diagnostic criteria can be useful (Box 1). A detailed discussion of gender terms and gender identity has been outlined in the Australian standards of care for TGD children and adolescents.[7]

While many TGD individuals will identify with a binary gender (ie, transgender male or transgender female), about 30% identify with a non-binary gender (Box 2).[3]

Rapid increases in demand for transgender health services have recently been reported worldwide.[3,8] Although international clinical practice guidelines exist,[9,10] recommendations are based on low level evidence, broad and open to interpretation. Additionally, there are differences internationally with availability, subsidy and access to medications. Medical training in transgender health care is lacking and 79% of Australian clinicians experienced in prescribing gender-affirming hormone therapy supported the development of local guidelines.[11] As such, we aim to provide specific recommendations for the hormonal and related management of TGD individuals aged over 18 years for Australian medical practitioners.

Methods

During the 2017 Australian Professional Association for Trans Health (AusPATH, formerly ANZPATH) Biennial Conference, the need for an Australian-based gender-affirming hormone-treatment pathway was highlighted. A working group was formed, chaired by the first author (AC). Members identified relevant evidence, published guidelines and expert opinion to develop the overview. There is an absence of randomised controlled trials in the field. Recommendations are based on low or very low level evidence and expert opinion, with authors placing a high value on harm minimisation and clinical need. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework has been used for key recommendations.[12] This approach classifies recommendations as strong (1) or weak (2) and evidence quality as high (A), moderate (B), low (C) or very low (D).[12] A survey of Australian TGD adult individuals was conducted to ascertain health needs, and results informed these guidelines. Australian prescribing patterns among the AusPATH membership were also ascertained by survey.[11] Controversies were resolved by discussion within the group. The draft statement was submitted to TGD community members, the AusPATH executive, the Endocrine Society of Australia (ESA) Medical Affairs Committee and the Royal Australasian College of Physicians (RACP) Policy and Advocacy Committee for feedback. The ESA and RACP invited external expert reviewers to provide comments, which were incorporated. The final version was endorsed by AusPATH, the ESA and the RACP.

Recommendations

Caring for gender diverse patients: general

Establishing and affirming an individual's gender identity and using the name and pronoun the person uses are vital for consultations and correspondence; legal identity markers can be used for Medicare purposes (GRADE: 1D). In addition to "she" or "he",

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Podcast with Ada Cheung available at https://www.mja.com.au/podcasts

1 ICD-11 diagnostic criteria for gender incongruence of adolescence or adulthood

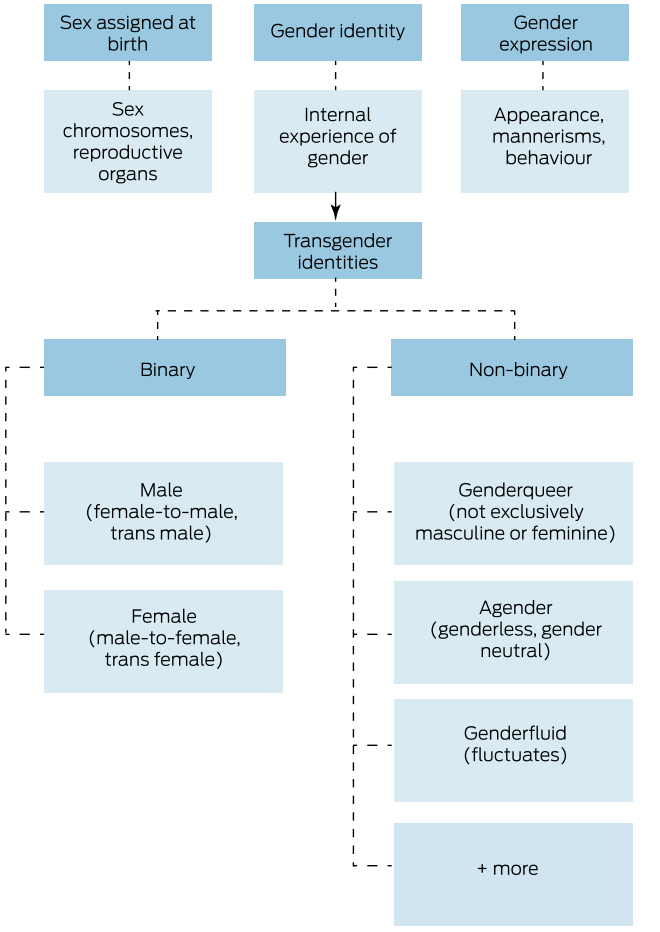
Gender incongruence of adolescence and adulthood is characterised by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, as manifested by at least two of the following:

- a strong dislike of or discomfort with one's primary or secondary sex characteristics (in adolescents, anticipated secondary sex characteristics) due to their incongruity with the experienced gender
- a strong desire to be rid of some or all of one's primary and/or secondary sex characteristics (in adolescents, anticipated secondary sex characteristics) due to their incongruity with the experienced gender
- a strong desire to have the primary and/or secondary sex characteristics of the experienced gender.

The individual experiences a strong desire to be treated (to live and be accepted) as a person of the experienced gender. The experienced gender incongruence must have been continuously present for at least several months. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

ICD-11 = International Classification of Diseases 11th Revision.[6] ◆

2 Distinction between gender identity, gender expression and sex assigned at birth



Gender identity and gender expression are distinct from biological sex. Although there are many gender identities,[7] transgender and gender diverse identities can be roughly separated into binary (ie, trangender male, transgender female) and non-binary. The term non-binary is used here as a broad umbrella category to describe identities which are outside of the binary; however, non-binary is also a specific gender identity. ◆

gender diverse individuals may use other pronouns (eg, "they") or no pronoun. Consideration should be given to gender neutral bathrooms and gender inclusive registration forms.

Management of TGD individuals ideally involves a multidisciplinary team (general practitioner, nurse specialist, psychologist, psychiatrist, endocrinologist, sexual health physician, gynaecologist, surgeon and speech pathologist as appropriate). Trained peer support workers can improve mental distress through facilitating access to support services, and provide advice on non-medical aspects of gender transition.

Not all who identify as TGD desire medical intervention. Many undergo social transition and change gender expression without medical intervention. Hormonal therapy with estradiol or testosterone will feminise or masculinise physical characteristics to align with an individual's gender identity (Box 3). Individual goals, especially for non-binary people, may be complex and treatment should be individualised; however, tailoring hormonal therapy to attain some characteristics and not others can be challenging.

Mental health review

A patient-centred yet holistic informed consent model of care is valid and Australian protocols exist.[13] These suggest a comprehensive mental health review by an experienced clinician (GP, physician, psychiatrist or psychologist) with adequate time to assess and support individuals seeking transition, to ensure that mental health concerns are appropriately treated and transition-related mood changes or stressors are managed[10,11] (GRADE: 1D). Mental health professionals play an important role in more complex cases, and can affirm capacity for informed consent and exclude less common conditions such as psychosis, dissociative identity disorder or body dysmorphic disorder.

Medical assessment

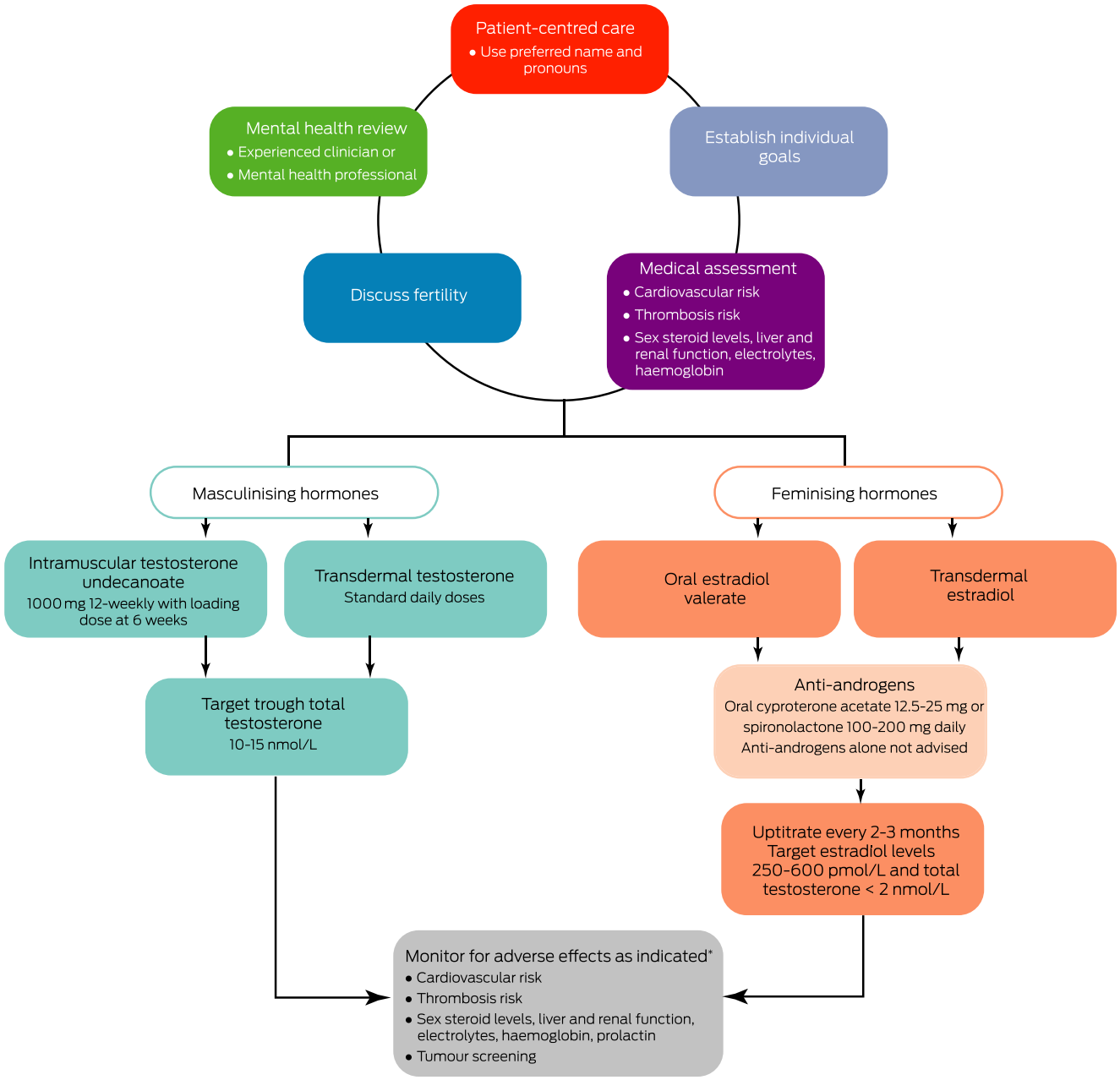
TGD individuals commonly self-report avoidance of medical care due to fear of discrimination.[14] A request for hormonal therapy can be an opportunity to provide routine medical care and preventive screening in addition to gender-affirming care. Relative contraindications to testosterone or estradiol therapy (such as polycythaemia, thrombosis, liver disease or cardiac failure) should be considered. There are insufficient data regarding the long term effects of hormonal therapy on cardiovascular outcomes.[15] A retrospective audit suggested that the most common cause of increased mortality in TGD people was cardiovascular disease.[16] Weight gain[17] and lipid derangements[15] may occur in individuals commencing hormone therapy, and smoking increases the risk of venous thrombosis at commencement of hormone therapy.[18] As a harm minimisation approach, we suggest assessing and mitigating cardiovascular risk factors.

Thrombosis risk may influence choice of estradiol preparation. Retrospective studies report a 5% incidence of venous thrombosis during estradiol therapy in TGD women, and incidence was highest with ethinyl estradiol use.[19,20] Thrombosis risk is greatest in the first year of treatment, and with smoking, obesity and increasing age (> 40 years).[21] Post-menopausal data suggest that transdermal estrogens carry minimal thrombotic risk.[22] Those at high risk should consider transdermal preparations and if thrombosis occurs, they should consider concurrent anticoagulation.[22]

In patients desiring hormone therapy, we recommend the following baseline investigations:[11]

- full blood examination — testosterone raises haematocrit levels and lowering testosterone lowers haematocrit levels;[23]

3 A suggested gender-affirming hormone therapy algorithm



* See Box 5. ◆

- liver function tests — estradiol is poorly metabolised in the setting of hepatic impairment; no changes in liver enzymes have been observed in transgender males;[24]
- electrolytes — hyperkalemia, although uncommon with normal renal function, can occur with spironolactone;
- fasting lipids and glucose — testosterone therapy lowers high density lipoprotein cholesterol levels, and raises triglyceride and low density lipoprotein cholesterol levels;[15] the effect of testosterone on insulin resistance is unclear,[25,26] although estradiol may worsen insulin resistance;[25]
- estradiol and total testosterone (see below).

Information regarding sexually transmitted infections, including human immunodeficiency virus pre-exposure prophylaxis, should be provided based on individual risk indicators.[27]

Chromosomal analyses are rarely abnormal in TGD individuals[28] and should only be performed if there is clinical suspicion (eg, Klinefelter syndrome). Genital examination is not routinely required.

While sex steroids are important in bone metabolism, a recent meta-analysis of TGD individuals showed no adverse effect on bone density.[29] Sex steroid deficiency due to pubertal suppression or following gonadectomy may accelerate bone loss. International guidelines recommend that bone mineral density measurement be considered in individuals with risk factors for osteoporosis, including subtherapeutic hormonal replacement.[10]

Medical therapy

Gender-affirming hormonal therapy in cohort and cross-sectional studies appears to improve psychological functioning,

quality of life, depression and suicidal ideation[30,31] (GRADE: 1C). A suggested algorithm is shown in Box 3.

Before hormonal treatment, we suggest that patients should understand the expected physical changes and time course of effects (Box 4), potential adverse effects (Box 5), and the irreversible nature of some changes (eg, voice lowering with testosterone). Most effects begin within a few months but maximal effects may take 2–3 years.

Hormonal therapy can impair fertility and patients should receive counselling. Sperm cryopreservation should be discussed before estradiol therapy due to expected changes in spermatogenesis. Oocyte storage can be considered; however, ovulation typically resumes on cessation of testosterone therapy. Testosterone is a teratogen and does not always prevent ovulation, so contraception should be discussed.

Masculinising hormone therapy. Standard replacement doses of testosterone are recommended to initiate masculinisation (GRADE: 1C). Doses can be adjusted to target trough total testosterone levels in the lower end of the male reference interval (10–15 nmol/L) (GRADE: 2D). The Pharmaceutical Benefits Scheme (PBS) criteria for androgen deficiency apply if gender markers are male or female. For people requiring masculinising hormone therapy for gender dysphoria, we use the authority indication "androgen deficiency due to an established testicular disorder". The patient must be treated by or in consultation (including teleconsult, phone or email) with a paediatrician, endocrinologist, urologist or sexual health physician. The specialist's name must be given in the authority application. Gender markers can be male or female.

The following testosterone formulations are available under the PBS:

- testosterone undecanoate 1000 mg, intramuscularly administered 12-weekly (with the first two doses 6 weeks apart);
- testosterone 1% (50 mg/5 g) gel sachets, applied transdermally, one sachet daily;
- testosterone 1% (12.5 mg/actuation) gel in pump pack, applied transdermally, four actuations daily — this preparation can be easily titrated;
- testosterone 5% (50 mg/mL) cream 2 mL, applied transdermally daily.

Testosterone enantate and testosterone esters are also non-PBS subsidised options.

Masculinising procedures. Testosterone therapy is highly effective at masculinising external appearance. Individuals may also desire surgery.[4] Options include:

- bilateral chest reconstruction mastectomy (colloquially known as "top surgery");
- hysterectomy ± oophorectomy;
- metoidioplasty (clitoral release and urethral lengthening — "bottom surgery");
- phalloplasty (penis creation — "bottom surgery").

Complication rates from metoidioplasty and phalloplasty are significant and outcomes may be suboptimal.[38] Gender-affirming surgery in the public sector in Australia is limited.

Chest binding is a common practice to tightly compress chest tissue, hiding the appearance of breasts. Severe skin irritation, pain, bruising and fractured ribs can result. Correctly sized, commercially purchased binders are recommended. Binders should be removed for sleep and use limited to 8–12 hours per day.[39]

4 Effects of feminising and masculinising hormone therapy

Feminising hormone effects	Masculinising hormone effects
Body fat redistribution	Body fat redistribution
Decreased muscle mass	Increased muscle mass
Softening of skin/decreased oiliness	Oily skin and acne
Decreased libido	Increased libido
Decreased spontaneous erections	Facial/body hair growth
Male sexual dysfunction	Male pattern baldness
Breast growth	Deepened voice
Decreased testicular volume	Vaginal atrophy
Decreased sperm production	Clitoral enlargement
Decreased growth of body and facial hair	Cessation of menses

Feminising hormone therapy. Estradiol therapy can be administered transdermally or orally. No data exist on gradual versus rapid titration or comparison of formulations in TGD individuals. Replicating female puberty, where estradiol levels gradually rise over 2 years, commencing at low doses with gradual uptitration every 2–3 months, is reasonable.[10] Typical full doses are oral estradiol or estradiol valerate 2–6 mg daily and transdermal estradiol patches 100–150 μg/24 hours changed twice weekly (GRADE: 1C). The adhesion of transdermal patches can be challenging in warm climates and in individuals with body hair.

Treatment should be adjusted based on clinical response; however, feminisation is typically slow (GRADE: 2D). The value of biochemical monitoring is uncertain; when performed, trough estradiol levels should be used. International guidelines recommend target estradiol levels 367–734 pmol/L; however, this is not based on any supportive data.[10] An Australian audit of 81 TGD individuals who had received estradiol therapy for over 6 months found that the mean estradiol level was 290 pmol/L with a median oral estradiol valerate dose of 6 mg daily.[40] We recommend targeting estradiol levels of 250–600 pmol/L and total testosterone levels < 2 nmol/L (ie, in the pre-menopausal female reference range) (GRADE: 2D). Individuals who wish to maintain erectile function may desire higher levels of testosterone; however, this will offset feminising effects.

High dose ethinyl estradiol (100 μg daily) was used until 1989 when retrospective audits showed increased risk of thromboembolic disease and possibly elevated risk of cardiovascular death.[41] These data underpin suggestions to avoid ethinyl estradiol.

Progestins. Despite anecdotal reports that progestins increase breast growth, no data support their use. Healthy postmenopausal women who received estradiol with progestins had increased risk of coronary heart disease compared with placebo[34] (not reported with estradiol alone[42]). Progestins can also increase risk of thrombosis, bloating, nausea and weight gain and are not recommended.[10] Cyproterone acetate, a commonly used anti-androgen agent, has progestogenic effects.

5 Possible risks and side effects of gender-affirming hormone treatment*

Type of therapy	Potential risks
Estradiol	Thromboembolic disease[19]
	Hypertriglyceridaemia[15]
	Prolactin elevation[32]
	Gall bladder disease[33]
	Cardiovascular disease[15,19]
	Breast cancer†
Testosterone	Polycythaemia[23]
	Acne[36]
	Sleep apnoea[37]
	Dyslipidaemia (increased triglyceride and LDL levels; decreased HDL levels)[15]

HDL = high density lipoprotein; LDL = low density lipoprotein. * This table provides an overview of risks associated with estradiol and testosterone therapy, some of which are extrapolated from cisgender populations. Long term data in TGD individuals are lacking. † An increased risk of breast cancer is seen with post-menopausal estrogen therapy in cisgender women, which increases with duration of use.[34] Owing to a lack of data, there are uncertainties regarding the risks of other hormone-dependent tumours[35] and cardiovascular disease.[15] ◆

Estradiol injections and implants. Therapeutic Goods Administration-approved estradiol injections and implants are not available in Australia. Estradiol injections or implants obtained from compounding pharmacies currently lack testing for potency, efficacy, safety and quality control.[43]

Anti-androgen therapy. Anti-androgens are often required in addition to estradiol therapy to lower endogenous testosterone levels or inhibit testosterone effects. Spironolactone (100–200 mg daily) or cyproterone acetate (12.5–25 mg daily) are both effective.[11] There are no comparative data. Both inhibit peripheral testosterone effects, but cyproterone acetate is also a potent progestin, suppressing gonadotrophins and testosterone production.[44] Cyproterone acetate may lower mood; however, it is unclear whether this is related to the drug, suppressed testosterone levels or interaction with the glucocorticoid receptor.[45] Case reports of meningioma[46] and prolactinoma[35] (or transient rises in serum prolactin[32]) have occurred with high dose cyproterone acetate (100–200 mg), and the lowest effective dose should be used.

Gonadotrophin-releasing hormone analogues are used as puberty blockers in adolescents, subsidised by specialist paediatric gender services. Due to lack of PBS subsidy, costs can be prohibitive.

Feminising procedures. Surgical options for feminisation include:

- vaginoplasty and orchidectomy ("bottom surgery");
- bilateral orchidectomy alone;
- breast augmentation ("top surgery") — breast development with estradiol can take up to 3 years but remains suboptimal in many;[47]
- facial feminisation surgery;
- chondrolaryngoplasty reduces the thyroid cartilage;
- laryngoplasty and vocal cord surgery can aid voice feminisation;
- estradiol therapy is typically ceased peri-operatively to avoid risk of thromboembolism; anti-androgens are not required following orchidectomy.

Voice training. Voice and communication are important aspects of gender expression and can contribute to dysphoria, particularly if vocal pitch results in misgendering.[48] Speech pathologists can provide feminising or masculinising voice training.

Facial and body hair. Changes to hair growth patterns from hormonal therapy can be slow due to hair follicle lifespan.[49] Permanent hair removal (laser or electrolysis) is often required. Preferred methods depend on hair colour and site, with advice best provided by hair removal professionals.

Genital tucking. Tucking is a frequent practice to minimise the appearance of the penis and scrotum. Similar to chest binding, skin irritation, infection, pain and bruising can result. Specialty designed garments or medical tape may alleviate risks; however, no data exist on the safety of tucking for prolonged periods.

Monitoring and support

While rigorous long term studies are required, retrospective cohort studies suggest that short term gender-affirming hormone therapy is safe, and significant benefits on mental health outweigh potential risks (GRADE: 1C). In the first year of treatment, 3-monthly monitoring is suggested to review clinical effects, sex steroid levels, mood changes and adverse effects, and provide general preventive screening[10,11] (GRADE: 2C). Mental health and spiritual and peer support can be beneficial during transition. Once stable, individuals can be reviewed less frequently (6–12 monthly). Weight gain may occur when commencing hormone therapy[17] and lifestyle advice is recommended. Smoking cessation should be encouraged. Cancer screening should be individualised based on the presence of organs in TGD individuals, not gender identity or hormonal therapy status.[35]

Polycythaemia with testosterone therapy

Haemoglobin levels should be compared with the male reference interval. If the haematocrit level is > 0.5,[10] exclude alternative causes (eg, smoking) and consider decreasing the testosterone dose or increasing the dosing interval.

Persistent menstruation on testosterone therapy

Menstrual suppression usually occurs within 1–6 months of testosterone therapy, but menses can continue beyond 12 months.[50] If menses result in significant dysphoria, options include increasing testosterone levels, oral progestins or progestin-releasing intrauterine devices.

Acne with testosterone therapy

Acne peaks at 6 months and gradually improves over time.[51] Topical retinoids or retinoid–benzoyl peroxide combinations are useful for mild to moderate acne. Moderate to severe acne may require oral antibiotics or isotretinoin.

Summary

Increasing numbers of TGD individuals are seeking health care in Australia and clinicians need to provide appropriate gender-affirming care. While pathways to gender transition are

individualised, hormonal therapy is effective at aligning physical characteristics with gender identity and improving dysphoria, quality of life and mental health. Further medical research is needed to guide clinical care and understand the long term effects of hormonal therapies.

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