Being transgender or gender diverse (TGD) is now viewed as part of the natural spectrum of human diversity. Estimates suggest that 0.1–2% of the population are TGD. 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. 1–3

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. 4 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. 5

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. 6–8 Although international clinical practice guidelines exist, 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. 10 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. 11 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 using the name and pronoun the person uses are vital for consultation and correspondence; legal identity markers can be used.
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.

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

<table>
<thead>
<tr>
<th>Gender assigned at birth</th>
<th>Gender identity</th>
<th>Gender expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex chromosomes, reproductive organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal experience of gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transgender identities</td>
<td></td>
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</tr>
</tbody>
</table>

- Binary (female-to-female, male-to-male)
- Non-binary (not exclusively masculine or feminine)
- Male (female-to-male, trans male)
- Female (male-to-female, trans female)
- Genderqueer (genderless, gender neutral)
- Genderfluid (fluctuates)
- + more

Gender identity and gender expression are distinct from biological sex. Although there are many gender identities, transgender and gender diverse identities can be roughly separated into binary (ie, transgender 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.

Mental health review

A patient-centred yet holistic informed consent model of care is valid and Australian protocols exist. 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 (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. 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. A retrospective audit suggested that the most common cause of increased mortality in TGD people was cardiovascular disease. Weight gain and lipid derangements may occur in individuals commencing hormone therapy, and smoking increases the risk of venous thrombosis at commencement of hormone therapy. 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. Thrombosis risk is greatest in the first year of treatment, and with smoking, obesity and increasing age (> 40 years). Post-menopausal data suggest that transdermal estrogens carry minimal thrombotic risk.

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

- full blood examination — testosterone raises haematocrit levels and lowering testosterone lowers haematocrit levels;
liver function tests — estradiol is poorly metabolised in the setting of hepatic impairment; no changes in liver enzymes have been observed in transgender males,

- 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, the effect of testosterone on insulin resistance is unclear,

- 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.

Chromosomal analyses are rarely abnormal in TGD individuals 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. 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.

Medical therapy

Gender-affirming hormonal therapy in cohort and cross-sectional studies appears to improve psychological functioning,
quality of life, depression and suicidal ideation\textsuperscript{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.\textsuperscript{1} 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.\textsuperscript{55} 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.\textsuperscript{39}

Feminising hormone therapy. Estradiol therapy can be administered transdermally or orally. No data exist on gradual versus rapid titration of comparison of formulations in TGD individuals. Replicating female puberty, where estradiol levels gradually rise over 2 years, commencing at low doses with gradual titration every 2–3 months, is reasonable.\textsuperscript{3} 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.\textsuperscript{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.\textsuperscript{35} 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.\textsuperscript{41} These data underpin suggestions to avoid ethinyl estradiol.

Progestins. Despite anecdotal reports that progestins increase breast growth, no data support their use. Healthy post-menopausal women who received estradiol with progestins had increased risk of coronary heart disease compared with placebo\textsuperscript{44} (not reported with estradiol alone\textsuperscript{53}). Progestins can also increase risk of thrombosis, bloating, nausea and weight gain and are not recommended.\textsuperscript{45} Cyproterone acetate, a commonly used anti-androgen agent, has progestogenic effects.
5 Possible risks and side effects of gender-affirming hormone treatment

<table>
<thead>
<tr>
<th>Type of therapy</th>
<th>Potential risks</th>
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<tbody>
<tr>
<td>Estradiol</td>
<td>Thromboembolic disease 19</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridaemia 15</td>
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<tr>
<td></td>
<td>Prolactin elevation 23</td>
</tr>
<tr>
<td></td>
<td>Gall bladder disease 33</td>
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<tr>
<td></td>
<td>Cardiovascular disease 15 39</td>
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<tr>
<td></td>
<td>Breast cancer 17</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Polycythaemia 23</td>
</tr>
<tr>
<td></td>
<td>Acne 16</td>
</tr>
<tr>
<td></td>
<td>Sleep apnoea 37</td>
</tr>
<tr>
<td></td>
<td>Dyslipidaemia (increased triglyceride and LDL levels; decreased HDL levels) 37</td>
</tr>
</tbody>
</table>

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. Owing to a lack of data, there are uncertainties regarding the risks of other hormone-dependent tumours and cardiovascular disease. 

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.

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. There are no comparative data. Both inhibit peripheral testosterone effects, but cyproterone acetate is also a potent progestin, suppressing gonadotrophins and testosterone production. 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. Case reports of meningioma and prolactinoma (or transient rises in serum prolactin) 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; 
- 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. 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. 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 (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 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.

Polycythaemia with testosterone therapy

Haemoglobin levels should be compared with the male reference interval. If the haematocrit level is > 0.5, 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. 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. 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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