Hormone therapy for trans and gender diverse patients in the general practice setting

Pauline Cundill

Background
In recent years there has been a significant increase in the number of trans, gender diverse and non-binary (TGDNB) people accessing healthcare. For many of these individuals the first port of call will be to their local general practitioner (GP). The TGDNB community is a high-priority population with the highest suicide rates of any population group in Australia. There is evidence that mental health outcomes improve significantly when individuals are able to access gender-affirming hormones.

Objective
The aim of this article is to provide GPs working in Australia with a practical guide to prescribe gender-affirming hormone therapy to TGDNB patients.

Discussion
GPs are ideally placed to provide care for TGDNB patients in the primary care setting. Gender incongruence is no longer viewed as a mental health disorder. In recent years there has been a move away from mandatory psychiatric assessment to more contemporary patient-centred models of care. TGDNB patients may present to their GPs requesting gender-affirming care, and this may include a request for gender-affirming hormones. It has become clear that reducing barriers to healthcare and providing earlier access to gender-affirming hormones improves the health outcomes and wellbeing of TGDNB people. However, significant numbers of people within the TGDNB community find themselves unable to access appropriate and timely medical services. In a recent national survey of TGDNB individuals, over half of the respondents reported their access to gender-affirming care as either ‘ok’, ‘poor’ or ‘non-existent’.

GPs throughout Australia are ideally placed to provide gender-affirming care to TGDNB patients. Gender-affirming hormones can be prescribed and monitored in a primary care setting in most cases. Several local resources have been developed to assist GPs to prescribe hormone therapies. Training and professional development activities are available, and mentoring by a colleague with experience working in the field is recommended.

General principles of prescribing gender-affirming hormones
The general principles of prescribing gender-affirming hormones can be summarised as follows.

- The goal of gender-affirming hormone therapy is to align physical appearance with gender identity to reduce distress and improve wellbeing.
- Hormone therapy should be individualised – there is no ‘one size fits all’.
- When prescribing hormone therapy, it is important to start with low doses and titrate up gradually.
- Gender-affirming hormone therapy is usually, but not always, lifelong. Some patients choose to cease hormones once the desired changes have occurred.
Informed consent model of care

In 2017 the Equinox Gender Diverse Health Centre in Melbourne (Thorne Harbour Health) produced the first Australian guideline for an ‘informed consent’ model of care, Protocols for the initiation of hormone therapy for trans and gender diverse patients. The guideline is based on a similar protocol that was successfully implemented in the USA. The guideline is endorsed by the Australian Professional Association for Transgender Health (AusPATH) and the Gender Clinic, Monash Health, Victoria. Under an informed consent model of care, the treating GP is the main care provider. There is an emphasis on self-determination, patient-centred care and mental health support. Mental health support can be provided by a counsellor, GP, psychologist, psychiatrist or peer worker depending on the patient’s needs. If the patient is unable to give informed consent or has severe unstable mental health concerns such as active psychosis, a psychiatry review is recommended prior to initiation of gender-affirming hormones.

Before initiating gender-affirming hormones, it is important to confirm a history of gender incongruence. This is self-determined by the patient. A patient will typically describe a persistent incongruence between their gender identity and their birth-assigned gender. It is important to spend time counselling the patient about hormone therapies and exploring their psychosocial situation and supports. This may be covered in a relatively short time or may require several consultations. The length of time required depends on the level of experience of the treating GP and the complexity of the presentation.

Pre-commencement visits provide an invaluable opportunity to provide preventive care, sexual health screening and general health checks. A suggested checklist for use prior to commencing gender-affirming hormones follows.

- Confirm history of gender incongruence (self-determined by the patient).
- Take a comprehensive medical history and family history to exclude contraindications to hormone therapies.
- Perform a mental health assessment and offer referral for counselling or peer support.
- Explore the patient’s ideas, concerns and expectations
  - What are their goals?
  - Do they have any concerns?
  - What are their expectations? Are they realistic?
- Discuss potential changes resulting from hormone use and an expected timeline for changes.
- Discuss potential complications and side effects of gender-affirming hormones.
- Check baseline blood pressure and body mass index.
- Organise baseline blood tests including follicle-stimulating hormone, luteinising hormone, oestradiol, total testosterone, full blood examination, urea and electrolytes, and liver function tests. Consider glycated haemoglobin and fasting lipids if the patient is aged >40 years or if additional cardiovascular risk factors are present.
- Offer referral for sperm-cryopreservation prior to commencement of feminising hormones.

### Table 1. Feminising hormones

<table>
<thead>
<tr>
<th>Feminising hormone</th>
<th>Typical initial dose</th>
<th>Typical maintenance dose</th>
<th>PBS listed</th>
<th>Practice tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol valerate tablets; oestradiol tablets</td>
<td>2 mg daily</td>
<td>6–8 mg daily</td>
<td>Yes</td>
<td>• Take once daily or in two divided doses.</td>
</tr>
<tr>
<td>Oestradiol patches</td>
<td>25–50 μg over 24 hours applied once weekly or every 3–4 days</td>
<td>100–200 μg over 24 hours applied once weekly or every 3–4 days</td>
<td>Yes</td>
<td>• Apply to clean dry skin on lower abdomen or buttocks. • Skin irritation may occur. • In warm humid climates, patches may not adhere.</td>
</tr>
<tr>
<td>Oestradiol gel sachet</td>
<td>1 mg daily</td>
<td>1–2 mg daily</td>
<td>Yes</td>
<td>• Apply to a ‘palm-sized’ area of the lower abdomen or thigh. If gel is applied to a larger body surface area, it may reduce effectiveness.</td>
</tr>
<tr>
<td>Oestradiol implant</td>
<td>100 mg (subcutaneous)</td>
<td>100 mg subcutaneous pellet every 6–9 months</td>
<td>No</td>
<td>• The implant can be accessed through a compounding pharmacy. • Oestradiol implants are not TGA approved. • Disposable trochars may be purchased online.</td>
</tr>
</tbody>
</table>

PBS, Pharmaceutical Benefits Scheme; TGA, Therapeutic Goods Administration
• Assess and document capacity to give informed consent. Regular clinical review is essential after commencement of gender-affirming hormones. Visits should include a mental health review, blood tests, blood pressure, body mass index, counselling and advice.

**Feminising hormones**

The most commonly prescribed feminising hormone for TGDNB people in Australia is oestradiol valerate. 12 Typical doses are outlined in Table 1. Ethinylestradiol is no longer the preferred option because of concerns it may confer a higher thrombotic risk. 13-14 Transdermal oestradiol is another option and is preferred over oral oestradiol for patients aged >40 years and those with risk factors for thromboembolic disease. Oestradiol subcutaneous implants are preferred by many patients; however, these products can be difficult to access in Australia and can be financially prohibitive as they are not available on the Pharmaceutical Benefits Scheme (PBS). Patients should be counselled that physical changes with oestrogen are likely to be slow and will vary between individuals.

Early changes with oestrogen include:

- calmer mood
- softer skin
- reduction in libido
- erectile dysfunction.

Changes that occur over the following six-to-twelve months include:

- body fat redistribution (a more curvy body shape)
- decreased muscle mass
- decreased testicular volume
- breast development (can take up to three years).

Oestrogen does not alter the voice. If their voice is causing distress, the patient can be offered a referral to a speech pathologist for voice feminisation therapy.

**Side effects**

Side effects of oestradiol are similar to those of the oral contraceptive pill. Nausea and weight gain may occur. More serious side effects include deep vein thrombosis, gallstones, infertility and liver impairment. Fertility is reduced soon after commencing oestrogen because of reduced spermatogenesis and atrophy of seminiferous tubules. 15 Sperm cryopreservation should be discussed prior to commencement of gender-affirming hormones. Smokers should be warned of the cumulative risk of smoking on thrombosis risk, and supported to quit.

**Monitoring**

Blood tests should be organised on a three-monthly basis during the first year, then six-to-twelve-monthly in the longer term to check oestradiol and testosterone levels, liver function, urea and electrolytes and full blood examination. There is ongoing debate about the optimum range for oestradiol levels in this setting. As a general guide, an oestradiol level in the cisfemale (non-transgender female) range of 300–800 pmol/L is reasonable. There can be considerable variability between oestradiol levels, and it is important not to become too fixated on ‘the levels’. If the patient is happy with how their transition is progressing, the dose does not necessarily need to be adjusted. It is important to ensure oestradiol levels are not too high (>1000 pmol/L) as this may predispose the patient to a higher risk of adverse effects. Non-binary patients may prefer a target oestradiol level between the male and female range.

Oestrogen therapy will usually suppress testosterone levels but often not to the desired level. In this case, the GP can consider prescribing an anti-androgen.

**Anti-androgens**

Anti-androgens are usually prescribed alongside oestradiol to reduce testosterone levels. The most commonly prescribed anti-androgens for gender transition in Australia are spironolactone and cyproterone acetate. 12

Typical doses are outlined in Table 2. Cyproterone acetate is a more potent anti-androgen than spironolactone 16 and has progestogenic properties. An Australian study is currently underway to ascertain the optimum cyproterone acetate dose in this setting (Dr J Dean, ‘GoLoCypro: Titrating the lowest effective dose of cyproterone acetate for treatment of trans and gender diverse people who request feminizing hormones [2019–2021]’, The University of Queensland).

Some people choose not to take an anti-androgen, including those who wish to preserve erectile function. Patients taking anti-androgens should be counselled that physical changes are likely to be slow and will vary between individuals.

Effects of anti-androgens include:

- slower growth of body hair
- reduction of acne
- reduction in libido
- erectile dysfunction.

Facial hair usually persists. Laser or electrolysis treatments may be indicated.

**Table 2. Anti-androgens**

<table>
<thead>
<tr>
<th>Anti-androgen</th>
<th>Typical initial dose</th>
<th>Typical maintenance dose</th>
<th>PBS listed</th>
<th>Practice tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone tablets</td>
<td>50 mg daily</td>
<td>100–200 mg daily</td>
<td>Yes</td>
<td>Monitor electrolytes and postural blood pressure.</td>
</tr>
<tr>
<td>Cyproterone acetate tablets</td>
<td>12.5–25 mg daily</td>
<td>12.5–50 mg daily</td>
<td>Yes</td>
<td>Monitor liver function and mood.</td>
</tr>
</tbody>
</table>

PBS, Pharmaceutical Benefits Scheme
Side effects
Patients often report feeling tired following commencement of anti-androgens. Spironolactone is usually well tolerated but can cause hyperkalaemia, postural hypotension and diuresis. Cyproterone acetate may exacerbate depression. Hepatotoxicity and meningioma have been reported with high doses of cyproterone.

Monitoring
For people desiring cisfemale hormone levels, hormone therapy should aim for a total testosterone level of <2 nmol/L. It is important to monitor electrolytes and liver function tests on a six-monthly basis. Spironolactone blocks peripheral testosterone receptors and therefore may be clinically effective even in the setting of a measured serum testosterone level above target. It is important to treat the patient according to their goals and not get too caught up in ‘the levels’.

Some TGDNB patients choose to undertake orchidectomy to avoid the need for anti-androgens. In this instance, it is important to continue oestradiol for bone protection.

Progesterone
Progesterone was routinely prescribed to transfeminine patients in past years when combined oral contraceptives were the standard of care. In recent years oestradiol has become the preferred option, and progesterone is less frequently prescribed. There is a lack of evidence of the efficacy of progesterone in this setting. Anecdotally, many patients report breast growth with progesterone, particularly when taken during the first two years of gender transition. If prescribing progesterone, a micronised product such as prometrium 100 mg orally daily could be considered. This is likely to have less adverse metabolic effects than synthetic progesterone. There is no need to cycle the progesterone. Patients should be warned of possible sedation with this product and advised to take it at night-time on an empty stomach.

Masculinising hormones
The most commonly prescribed masculinising hormone for gender affirmation in Australia is testosterone undecanoate. Other options include fortnightly depot testosterone injections and transdermal preparations, outlined in Table 3. Fortnightly injections have become less popular in recent years because of the resultant peaks and troughs of testosterone levels and the potential for mood lability. Transdermal testosterone is a good option for patients who are needle phobic or prefer the convenience of a topical product. The gels tend to be sticky and can take several minutes to absorb.

In contrast to feminising hormones, testosterone can cause physical changes

<table>
<thead>
<tr>
<th>Masculinising hormone</th>
<th>Typical initial dose</th>
<th>Typical maintenance dose</th>
<th>PBS listed</th>
<th>Practice tips</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate injection</td>
<td>1000 mg IMI, with the first two doses administered six weeks apart as a loading dose</td>
<td>1000 mg IMI every 12 weeks</td>
<td>Yes, authority required</td>
<td>• Administration occurs via slow deep IMI to the upper outer quadrant of buttock with a 21G needle.</td>
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<td></td>
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<td></td>
<td></td>
<td>• Choice of needle length should take into account patient size.</td>
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<td></td>
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<td></td>
<td>• If administered subcutaneously, it may cause a painful lump around the injection site.</td>
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<td></td>
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<td></td>
<td></td>
<td>• Self-administration is not recommended.</td>
</tr>
<tr>
<td>Testosterone enantate injection; testosterone esters injection</td>
<td>125 mg IMI every two weeks</td>
<td>250 mg IMI every two weeks</td>
<td>No</td>
<td>• Administration occurs via slow deep IMI to the upper outer quadrant of buttock or anterolateral thigh with a 21G needle.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• It is relatively easy to administer; patients may prefer to self-administer.</td>
</tr>
<tr>
<td>Testosterone gel sachets 1% (50 mg/5 g)</td>
<td>One sachet every day or alternate days</td>
<td>One sachet daily</td>
<td>Yes, authority required</td>
<td>• Product may potentially transfer to partners.</td>
</tr>
<tr>
<td>Testosterone gel pump pack (12.5 mg/actuation)</td>
<td>1-2 pumps daily</td>
<td>Four pumps daily</td>
<td></td>
<td>• These preparations are easy to titrate.</td>
</tr>
<tr>
<td>Testosterone cream 5% (50 mg/mL)</td>
<td>1-2 mL daily</td>
<td>2 mL daily</td>
<td></td>
<td>• These preparations are useful for patients who request low doses for partial masculinisation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Testosterone cream 2% is available; however, there is no PBS subsidy.</td>
</tr>
</tbody>
</table>

IMI, intramuscular injection; PBS, Pharmaceutical Benefits Scheme
relatively quickly, and patients should be counselled to this effect. Within six months of commencement of masculinising hormones, the patient’s appearance will usually be much changed.

Early changes with testosterone include:
- acne
- oily skin
- increased libido
- increase in clitoral size.

Changes that occur over the following six-to-twelve months include:
- amenorrhoea
- body fat redistribution
- muscle growth
- increase in body and facial hair
- voice deepening.

Side effects
Side effects of testosterone include weight gain, androgenic alopecia, sleep apnoea and polycythaemia. Acne is common, particularly during the first two years after initiation of testosterone. The usual treatment measures can be used for acne in this context, including topical therapies, tetracyclines or referral for isotretinoin.

Voice deepening with testosterone is usually irreversible. Some patients report ‘vocal fatigue’ with testosterone, which is a tiring and hoarseness of the voice that worsens throughout the day. This is particularly relevant in occupations where voice projection is required, and speech pathology referral may be considered.

Vaginal irritation due to atrophic vaginitis is commonly encountered. A twice-weekly 10 μg vaginal oestradial pessary may be acceptable to the patient and will often reduce symptoms.

As a result of concerns about fertility, TGDNB patients are often advised to freeze oocytes prior to gender transition. This is probably unnecessary as ovulation and menstruation typically resume on cessation of testosterone. Many transmasculine people cease testosterone temporarily in order to start a family, either by harvesting and donating eggs or by carrying a biological child.

Monitoring
It is recommended that full blood examination, liver function and testosterone levels are checked six-monthly. After initiation of testosterone, haemoglobin and haematocrit levels will usually increase. If the haematocrit level exceeds 0.5 (50%), the patient may be at an increased risk of a thrombotic event. Strategies to lower haematocrit level include extending the interval between injections, reducing the dose or switching to an alternative testosterone product. If polycythaemia persists, referral to a haematologist for therapeutic venesection is recommended.

For patients desiring testosterone levels in the cismale (non-transgender male) range, hormone therapy should aim for a trough total testosterone level of 10–15 nmol/L. Levels are usually checked just prior to a testosterone injection or 24 hours after application of a transdermal preparation. There is a lack of data regarding long-term effects of testosterone in the TGDNB setting. Patients should be advised to cease smoking, exercise regularly and optimise body mass index. It is important to monitor lipids, particularly if other cardiovascular risk factors are present.

If mood irritability or fatigue is experienced towards the end of the injection interval, consideration can be given to reducing the injection interval.

Testosterone should not be relied on for contraception as breakthrough ovulation may occur. However, contraceptives containing oestrogen should generally be avoided for transmasculine patients. A useful statement outlining contraception choices for TGDNB people is available from the Faculty of Sexual and Reproductive Healthcare, UK.

Children and adolescents
For patients <16 years of age, consideration of puberty blockers and gender-affirming hormones generally occurs in a tertiary setting. Australian standards of care and treatment guidelines for trans and gender diverse children and adolescents are available. Long waiting times are usually encountered. GPs can assist these patients by providing a safe, inclusive and welcoming practice environment and offering mental health support. For patients with dysphoria relating to menstruation, a prescription of norethisterone 5 mg orally twice daily may provide temporary amenorrhoea and reduce distress.

Conclusion
There have been many advances in the field of transgender health. Gender diversity is no longer considered a mental health disorder, and new pathways of care have been developed. GPs are ideally placed to provide gender-affirming care in the primary care setting.

Key points
- GPs are likely to encounter TGDNB patients in their daily practice.
- GPs can initiate gender-affirming hormones for adults under an ‘informed consent model of care’ in most cases.
- Several resources exist to assist GPs to upskill in the prescription and monitoring of gender-affirming hormones.

Resources
- Northwest Melbourne Primary Health network – Primary health care for trans, gender diverse & non-binary people
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Competing interests: PC was a co-author of the ‘informed consent guideline’ in 2017 (Protocols for the initiation of hormone therapy for trans and gender diverse patients). This guideline was written by a group of general practitioners and other specialists working in the field, and community representatives. The guideline was endorsed by the Australian Professional Association for Transgender Health (AusPATH) and the Gender Clinic, Monash Health.
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References
2. Fisher CM, Waling A, Kerr L, et al. 6th national Darwin region. The author acknowledges that they live and work on Larrakia land, and acknowledges the Larrakia people as the traditional custodians of the Darwin and outer Darwin region.

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