Long term hormonal treatment for transgender people

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What you need to know

Transgender people using hormone treatment need lifelong medical support and care. Hormonal treatment for gender dysphoria resembles hormone replacement therapy for people with hypogonadism.

Hormone treatment in transgender people is accepted to be safe and increases overall wellbeing in most people. The most common (though rare) side effects are venous thrombosis in trans women due to oestrogens and polycythaemia caused by androgens in trans men.

Some trans women will not have had their prostate removed and some trans men keep their ovaries. Be aware of the risk of cancer in these sites and think about the added risk of hormone supplementation.

The aim of hormone treatment in transgender people is to adjust their secondary sex characteristics to be more congruent with their experienced gender. Hormone treatment for transgender people is usually initiated by specialist gender clinics, but some people start hormone treatment of their own accord without a prescription. With growing numbers of transgender people presenting to healthcare services (estimated as 9.2 per 100 0001), general practitioners, general endocrinologists, and other doctors will become increasingly involved in their long term care, the prescription of hormones, and consideration of potential side effects. Several guidelines are available on the start of hormonal treatment2-7; the focus of this article is the long term hormonal care for transgender people who might no longer attend a specialist clinic. It is aimed at a more general readership of physicians occasionally seeing adult transgender people.

Transgender terminology

Language and terminology are sensitive. Some terms used in the past are no longer appropriate because they might have negative connotations.

Sex/gender

The term gender has historically been used to refer to psychological, behavioural, and sociological characteristics, and their categorisation by society as “masculine” or “feminine.” The term sex has historically been used to refer to biological characteristics similarly categorised. Transgender people stress the importance of proper language that respects their identity. Terms like male-to-female transgender or cross-sex hormonal therapy might therefore not be appropriate because they suppose a binary view. Even the distinction between gender and sex might be perceived as an oversimplification. Be sensitive to a person’s own use of terminology and interpretation of their identity. If in doubt, ask your patient what language they prefer.

Trans woman

A woman who was assigned male at birth.

Trans man

A man who was assigned female at birth.

In this article we use these terms also for people who identify as non-binary and/or wish for partial changes. Attending physicians should be aware of possible medical problems resulting from biological aspects of the sex at birth. For example, prostate cancer in a trans woman.

Non-binary/Gender-queer

The terms “non-binary” and “gender-queer” are used by people who do not exclusively identify as man or woman, masculine or feminine, male or female.

Anti-androgens

Agents antagonising testosterone action.

Anti-gonadotropics

Agents that inhibit secretion of luteinising and follicle stimulating hormones from the pituitary.

Hormone treatment in transgender people

Many transgender people seek to adjust their physique to be more congruent with their experienced gender by using hormone treatments and/or undergoing surgical interventions. The broad aims of hormone treatment in adult transgender people are to eliminate as far as desired the earlier hormonal effects of the
sex steroids of their sex at birth and to induce the desired secondary sex characteristics of the experienced gender. Hormone preparations that are used in transgender medicine for gender dysphoria are the same that are used in gonadal endocrinology, although they are usually not licensed for treating gender dysphoria in itself. Table 1 lists these preparations. Hormones induce more than one effect. Oestrogens, for example, influence breast growth, bone density, skin, and the clotting system. Generally, it is not possible to selectively stimulate one effect and inhibit another. The effects of gonadal hormones can differ between persons because of the individual properties of the hormone receptors. Some people show a clear change in fat distribution pattern but little breast development, while in others the opposite occurs. In general, regular hormone treatment is needed for two to three years to reach its effect.1

**Hormone treatment for trans women**

**Oestrogen**

The key element in treating trans women is the administration of oestrogens. Guidelines recommend using the natural form 17β-oestradiol because ethinyleoestrogen (common in oral contraceptives) has been associated with a strong increase in the risk of venous thrombosis and cardiovascular disease.8 Progestogens cause no additional feminisation effect when prescribed alongside oestrogens.

**Anti-androgen**

In some people, oestrogen administration only suppresses testosterone below the upper level of cis (ie, persons for whom their gender identity matches their sex at birth). To achieve full suppression in all people, most guidelines recommend the use of oestrogen in combination with a testosterone suppressing agent.7 Testosterone suppressing agents (or anti-androgens) of several pharmacological classes are available (table 1). GnRH agonists are effective but more expensive (€100-150 per month). They are first line treatment in the UK. Cyproterone acetate combines anti-androgenic and anti-gonadotropic effects and is widely used in continental Europe. Spironolactone is an aldosterone antagonist with anti-androgenic properties and is used as anti-androgen primarily in the US. A recent study showed comparable effect of GnRH analogues instead of cyproterone acetate in suppressing testosterone levels.9 If trans women have undergone orchidectomy (as part of the surgical reassignment), anti-testosterone treatment could be stopped.

**Clinical effect**

Important effects of combined oestrogen and anti-testosterone treatment include breast development, softer skin, loss of sexual hair growth, increase in fat mass, broader hips, a decrease of lean body mass, and a decrease or change in libido with clinically relevant mood changes.7 Not all effects are as strong in every person. Sometimes, additional measures are needed to achieve the desired effects, such as laser and electrolysis to remove unwanted hair, or breast augmentation to achieve sufficient breast volume.

**Hormone treatment for trans men**

**Testosterone**

In trans men, testosterone is the key hormone administered and no anti-oestrogens are needed.4 Testosterone is converted to oestradiol (by aromatase activity in fat cells) in men and women and oestradiol plays an important role in bone physiology in cis men and trans men.10

**Clinical effect**

Important effects of testosterone are an increase in lean body mass and muscle strength, body and hair growth in a male pattern, and lowering of the voice. Testosterone supplementation given in the doses in table 1 leads to cessation of monthly periods. If uterine bleeding persists, a GnRH agonist or progestin ( lynestrenol 5 mg daily or medroxyprogesterone 10 mg three times daily or another progestin) could be added to stop uterine bleeding.

**Principles of dosing**

Most guidelines state that dosing of hormones should be guided by blood levels of oestradiol and testosterone, based on mean levels of the desired gender. These levels are often achieved with the dosages mentioned above; however, hormone levels are not a goal in themselves. The primary goals are usually a degree of feminisation or masculinisation as specified by the patient, which are achieved with their fullest effects after two to five years, similar to the temporal pattern of hormonal puberty. After this period, the goal for hormonal treatment—especially if in the meantime the gonads have been removed—might be to avoid signs and symptoms of hypogonadism such as mood changes, fatigue, osteoporosis, and muscle weakness. While dosage advice and target levels are an aid to avoiding underdosing and overdosing, one should be aware that, due to hormone receptor properties, similar levels can have different biological effects in different individuals, and different individuals can have different ideas about the desired outcome. In other words: the clinical effects and wellbeing of the trans person are paramount, not the hormone levels themselves. This applies also to persons who do not fit in the male/female distinction (non-binary or gender queer). It is possible to achieve hormone levels that are in between male and female reference ranges for both testosterone and oestradiol, but it is important to avoid hypogonadism in patients that already have gonadectomy in order to prevent bone loss and other consequences of hypogonadism.

**How well does it work and how safe is it?**

It has been shown that hormone treatment in transgender people with gender dysphoria increases wellbeing in most people.12 From a medical point of view, hormonal treatment seems to be acceptably safe.13

**Oestrogen**

Oestrogens increases the risk of venous thrombosis, but a study in trans women showed that long term treatment with oestrogen yields only a low thrombotic risk (one event in 1,286 person years).16 Oral oestradiol supplementation has a more prothrombotic effect than parenteral oestradiol supplementation; therefore it might be recommended to use parenteral supplementation in people with a higher risk for venous thrombosis (ie, family history of thrombosis or age over 50).17

**Anti-androgen**

Testosterone-blockers can have their own side effects, such as hyperprolactinaemia16 and an increased risk for meningioma with cyproterone acetate (although still very rare),18 and high potassium levels with spironolactone.

**Testosterone**

Testosterone supplementation increases the haematocrit into the male reference range and can sometimes lead to
polycythemia; therefore monitoring haematocrit is recommended every three months in the first year and then one to two times per year. Liver toxicity of testosterone has been described but is rare, and no liver function tests are recommended.

**Bone and cardiovascular disease**

Bone density can be affected, but both testosterone and oestrogen in recommended dosages lead to an increase in bone density. In general, oestradiol for trans women has a beneficial effect on cardiovascular risk factors, while testosterone for trans men has a detrimental effect. But limited experience points in the opposite direction for cardiovascular disease itself: an increase in cardiovascular disease in oestrogen users (particularly ethinyl oestradiol) and decrease in testosterone users. No clear explanations for this paradoxical finding are available yet.

**Malignancies**

Cases of cancer of the prostate and breast have been reported but recent studies showed no increased overall risk, although the estimated breast cancer risk in trans women is 33 times higher compared with cis men. However, much of what we know about the effects of hormone treatment in transgender people is from relatively small studies (table 2). Large, well designed studies, particularly in ageing subjects, are urgently needed to collect reliable estimates on effects and side effects.

**Long term follow-up**

Hormone supplementation is in principle lifelong, and people benefit from regular (yearly or two yearly) supervision by a doctor with an understanding of transgender health and hormone prescription. Follow-up might take place in a specialist gender clinic, or with a primary care physician or other generalist with sufficient training in hormonal supplementation. Long term follow-up would include checking the hormone levels in trans men and trans women and haematocrit in trans men at every visit (yearly or two yearly). Other measurements must be guided by risk factors of the individual, such as blood lipids in case of cardiovascular risk. If there are sex specific laboratory reference values, use the reference values of the person’s new gender. An exception is bone density measurement. From puberty on there are sex specific increases in bone mineral density, and reference values of the sex at birth should be used for assessment of T and Z values.

Trans women can develop prostate cancer, and breast cancer can develop in minimal residual breast cells in trans men. It would be important to consider and discuss withdrawal of hormonal treatment in these situations. We advise following the local guidelines for population screening of the cis population according to the relevant anatomy present (either prostate, cervix, or breasts).

**Transgender elderly**

Sex hormones rise in puberty. There is a sharp drop at menopause in women and a more gradual decrease in men. Data are lacking on whether to follow these patterns in transgender people. Many transgender people prefer to continue hormone use. The side effects of prolonged supplementation at dosages that induce young adult levels are not well studied. In our view, it seems prudent to taper the dose at increasing age, but there are no clinical data to support or dissuade from this approach. It is important, therefore, to discuss this uncertainty with the person and frame it in a general discussion about their overall health.

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**Case Vignettes**

**Vignette 1**

A 36 year old trans man comes for his biannual visit to his endocrinologist. He started testosterone injections (250 mg every two weeks) eight years ago. He is feeling well, works as a bus driver, and smokes 20 cigarettes a day. His blood tests show testosterone of 15 nmol/L just before the next injections. Haematocrit is 0.55.

**To consider**

The definition of polycythemia in terms of haematocrit levels differs among registries. From puberty on there are sex specific increases in bone mineral density, and reference values of the sex at birth should be used for assessment of T and Z values. Trans women can develop prostate cancer, and breast cancer can develop in minimal residual breast cells in trans men. It would be important to consider and discuss withdrawal of hormonal treatment in these situations. We advise following the local guidelines for population screening of the cis population according to the relevant anatomy present (either prostate, cervix, or breasts).

**Vignette 2**

A 66 year old trans woman comes to her general practitioner. She started oral oestradiol (4 mg daily) 10 years ago together with an anti-androgen (cyproterone acetate 50 mg daily). She decided not to have a vaginoplasty because of the risk of complications of her obesity (she has a body mass index of 40). Two weeks ago, she was diagnosed with a deep vein thrombosis of the left leg and she commenced warfarin. She now wonders if she should stop her hormone treatment.

**How this article was made**

A first draft was written by Mdh and LG with focus on long term hormonal treatment. We performed a search in www.pubmed.gov with search term “transgender OR transsexual” and “hormones OR oestrogen OR testosterone,” which revealed 485 papers. We largely focused on papers that were published in English in the last five years. AB was asked to join us as author to enhance the patient perspective. Our first version was extensively reviewed by five reviewers (including a trans person) and the BMJ editor. Their comments were very helpful in improving and clarifying the manuscript. They helped us to broaden the scope to practices used in other countries as well.

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**How patients were involved in the creation of this article**

Our author group includes a trans person. The review group included a trans person. AB was asked to join us as author to enhance the patient perspective. AB is trans man with 20 years of experience taking hormonal therapy. Our first version was extensively reviewed by five reviewers (including a trans person). Their comments helped us to improve the manuscript, especially in the use of sensitive phrasing.

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**Education into practice**

How confident do you feel about discussing hormone treatment with trans people in your practice?

- Are you aware of any resources that might support you with their longer term care?
- What might you do differently as a result of reading this article?

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### Tables

#### Table 1: Hormones used in transgender persons with typical doses in adults (20-50 years)

<table>
<thead>
<tr>
<th>Hormones used in transgender persons</th>
<th>Tablets</th>
<th>2-4 mg daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>Patch</td>
<td>100 ug/24 h</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>Gel 0.06%</td>
<td>1.5 mg (2.5 gr gel) daily</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Gel 10 mg/mL</td>
<td>50 mg/day</td>
</tr>
<tr>
<td>Testosterone</td>
<td>IM injections</td>
<td>250 mg/2-3 wk</td>
</tr>
<tr>
<td>Testosterone</td>
<td>IM injections</td>
<td>1000 mg/3 months</td>
</tr>
<tr>
<td>Gonadotropin releasing hormone (GnRH) analogues</td>
<td>Subcutaneous</td>
<td>3.75 mg/4 weeks or 11.25 mg/3 months</td>
</tr>
<tr>
<td>Testosterone blockers</td>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Tablets</td>
<td>100-300 mg per day</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Tablets</td>
<td>25-50 mg per day</td>
</tr>
</tbody>
</table>

The given doses and dose intervals are an indication. As stated in the text, both should be individualised.

IM: Intramuscular
### Table 2 Possible areas of concern in the long term follow-up of transgender persons on hormonal treatment and practical recommendations

<table>
<thead>
<tr>
<th>Area</th>
<th>Potential Concerns</th>
<th>Practical Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General health and wellbeing</strong></td>
<td>Fatigue and depressed mood are common signs of hypogonadism</td>
<td>Hormone treatment has not been associated with an increased risk for diabetes. Hormonal treatment might be responsible for some weight gain (average 3 kg)20</td>
</tr>
<tr>
<td><strong>Diabetes and metabolic health</strong></td>
<td>Hormone treatment has not been associated with an increased risk for diabetes. Hormonal treatment might be responsible for some weight gain (average 3 kg)20</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular disease</strong></td>
<td>Although oestrogens have beneficial effects on most classical risk factors of cardiovascular disease, the risk for cardiovascular disease itself seems to be increased.23 24 Cardiovascular risk management is recommended and body weight and BMI considered for all trans people on hormone treatment.</td>
<td></td>
</tr>
<tr>
<td><strong>Venous thrombosis</strong></td>
<td>Oestrogens in physiologic doses are associated with some increased risk of venous thrombosis.19 The use of ethinyl oestradiol should be discouraged because the risk is higher compared with oestradiol</td>
<td></td>
</tr>
<tr>
<td><strong>Osteoporosis</strong></td>
<td>Hormonal treatment itself is not associated with osteoporosis25 but non-compliance with lifetime hormonal substitution after gonadectomy has a detrimental effect on bone density and quality. Besides this, many transgender persons have lower bone mineral density already before starting hormonal treatment, possibly because they have lower levels of vitamin D.27 Checking bone density once in five years seems reasonable, especially when non-compliance is expected. In osteopaenic individuals, calcium and vitamin D supplementation together with lifestyle recommendation is warranted</td>
<td></td>
</tr>
<tr>
<td><strong>Haematocrit</strong></td>
<td>Testosterone induces erythrocytosis and might cause polycythaemia (haematocrit &gt;0.52), particularly with short term injections.8 16 Other factors might aggravate the polycythaemia (for instance smoking, chronic obstructive pulmonary syndrome). In the case of polycythaemia, quitting smoking is the first step. Testosterone gels might be more suited, and tapering of the dose might be warranted</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Older studies showed elevation of liver enzymes, especially in men using alkylated testosterone. This is rarely seen with the current hormonal regimens</td>
<td></td>
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<tr>
<td><strong>Hormone sensitive tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td>The risk for breast cancer in trans women is not higher compared with cis women. Access to breast cancer screening is warranted. In trans men, breast cancer might occur after mastectomy in residual breast cells24 25</td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian cancer</strong></td>
<td>In trans men not having undergone oophorectomy ovarian cancer might occur. Testosterone supplementation seems not to increase the risk, but data are sparse.</td>
<td></td>
</tr>
<tr>
<td><strong>Prolactinoma</strong></td>
<td>There is literature reporting prolactinomas in trans women, but no proof of increased risk exists.19 Cyproterone acetate increases prolactin levels, but is not used often in the long term. Regular checking of prolactin seems not to be indicated</td>
<td></td>
</tr>
<tr>
<td><strong>Prostate cancer</strong></td>
<td>Trans women retain their prostate after surgical gender confirmation. The risk of prostate cancer is low but not absent.27 28 The yield of regular checking of prostate by palpation or prostate specific antigen determination seems to be low</td>
<td></td>
</tr>
</tbody>
</table>