Recommendations of endocrine treatment for patients with gender dysphoria

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The purpose of this paper is to provide an objective and independent review of all published papers providing clinical guidelines in the hormonal and medical care of patients with gender dysphoria and transsexualism and to suggest safe modern prescribing guidelines. A computerised search of the published literature was performed using the MEDLINE, EMBASE and PsycINFO databases between 1998 and 2008. In addition, textbooks relating to the subject were reviewed. There are major similarities between various international clinical centres on the practice of therapeutics and risk management on hormone treatment for transsexual people. Most of the evidence comes from observational studies and older case reports. The mainstay of hormone treatment for the male to female trans person is estrogens and either a gonadotrophin releasing hormone (GnRH) agonist or anti-androgens. The main components of that for the female to male trans-person are testosterone and a GnRH agonist. Ongoing physical monitoring is important to maximize the benefits and minimise the risks associated with the treatment. More research is necessary to improve evidence-based practice in this area and especially the potential benefit of GnRH agonists for both trans women and men.

Keywords: gender dysphoria; hormones; estrogen; testosterone; endocrinology; gonadotrophin; guidelines

Introduction

The term gender dysphoria is known as transsexualism in the International Classification of Diseases-10 (World Health Organisation, 1992), which defines the condition as ‘the desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make the body as congruent as possible with the preferred sex through surgery and hormone treatment. The transsexual identity should be present persistently for at least two years in duration’. The same state is called Gender Identity Disorder in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000), where it is described as ‘the strong and persistent cross gender identification and a persistent discomfort with the sex and a sense of the inappropriateness of the gender role’. Treatments aim to improve quality of life, with psychological support, hormone therapy and surgical

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treatment alongside ‘real life experience’ where a trans woman would become used to living in the female gender role and vice versa for trans men. With regard to hormone therapy, with the exception of Sustanon in the UK (within the Summary of Product Characteristics), none of the prescribed sex hormone products are currently licensed for transsexualism (Tugnet, Goddard, Vickery, Khoosal, & Terry, 2007) therefore our aim is to provide an objective and independent review of all published papers providing clinical guidelines in the hormonal and medical care of patients with this condition.

World Professional Association for Transgender Health Standards of Care

The international society World Professional Association for Transgender Health (WPATH) formerly known as Harry Benjamin International Gender Dysphoria Association (HBIGDA), has created a sixth version of the Standards of Care. The principal purpose is to ensure that people with gender dysphoria enter an appropriate treatment program, which includes ongoing psychiatric or psychological monitoring, possibly endocrine treatment and, depending on the outcome of a period of cross-gender living (referred to as real life experience), gender confirmation surgical procedures. The philosophy of treatment is to try reversible procedures before those that are irreversible (Green, 2000). The sixth version of the Standard of Care for Gender Identity Disorders (Meyer, Bockting, Cohen-Kettenis, Coleman, DiCeglie, et al., 2001), established the guidelines on standard of care for both sexes as follows.

Requirements for cross-sex hormone therapy in adults. These are: age > 18 years; knowledge of what hormones can and cannot do and their social benefits and risks; a period of real-life experience for over three months or a period of psychotherapy lasting at least three months; and a letter of recommendation from a mental health professional to the prescribing physician.

Requirements for genital reconstructive surgery. These are: legal age of majority (in the UK the age of consent is usually taken as 16 years of age but adulthood commences at age 18 years); 12 months of continuous hormone therapy for those without contraindication; 12 months of successful full-time, real-life experience as the appropriate gender; regular participation in psychotherapy (if required by the mental health professional); knowledge of the cost and likely complications of surgical treatment; awareness of different competencies of surgeons; and two letters of recommendation from mental health professionals.

Methods

A computerised search of the published literature was performed using the MEDLINE, EMBASE and PsycINFO databases between 1998 and 2008. The keywords used in the search were transsexual, transsexualism, gender dysphoria, transgender, gender identity disorder, hormone treatment, clinical trial and combinations of the above. There was a large overlap of papers found in MEDLINE, EMBASE and PsycINFO. On review we found a total of 15 most relevant papers. Each paper was read by at least two of the authors and where additional references were cited these were obtained and added to the total number of papers. This led to a final sample of 20 relevant papers. In addition, textbooks relating to the topic were reviewed.
We looked particularly for advice about gonadotrophin releasing hormone (GnRH) agonists, which initially stimulate and then depress luteinising hormone release by the pituitary gland. These agents reduce the concentration of serum testosterone into the castrate range within one week of administration in biological men and stop the ovaries from making estrogen in biological women. Examples include buserelin, goserelin, leuprorelin and triptorelin.

The papers were reviewed and categorised as involving treatment for trans women (male-to-female transition) and trans men (female-to-male transition).

**Trans women**

*The basis of treatment*

The role of oestrogens in the biological female is multifactorial and oestrogens have an effect on almost every part of the individual. As well as contributing to feminisation, they decrease plasma cholesterol formation, uphold bone mineral deposition and maintain libido (Greenspan & Gardner, 2004). In trans women, over a period of 3–36 months, oestrogens will soften the skin, stimulate breast development and cause a more feminine redistribution of fat (developed breast tissue will remain even if estrogen is stopped: Dahl, Feldman, Goldberg, & Jaberi, 2006). Both estrogens and antiandrogens cause suppression of testosterone and its effects, thereby reducing erection. After a period of 6–36 months, they will also reduce body hair growth although not stop it completely. Electrolysis or laser hair removal may therefore also be desired, especially on the face. Oestrogens and antiandrogens have synergistic effect and, hence, will augment the effect of each other. Voice pitch and speech patterns will not change with hormones. Training from a speech (voice) and language therapist can make these more feminine. Finally, laryngeal prominence or ‘Adam’s apple’ will not shrink with hormones (Dahl et al., 2006) and would require surgery to achieve a feminine appearance.

The side-effects expected from oestrogens are: an increased risk of venous thrombosis; nausea and vomiting; impaired liver function; increased risk of gallstones; depression; infertility; dry skin and brittle nails; headaches/migraine (Dahl et al., 2006); and decreased glucose tolerance. There can also be increased levels of prolactin and three cases of benign prolactinomas have been reported (Moore, Wisniewski, & Dobs, 2003). Although it is not known if taking oestrogens increases the risk of breast cancer in trans women (Dahl et al., 2006), four cases of breast cancer have been reported (Seal, 2007). Three cases of prostate cancer are known, although whether this is related to taking long-term oestrogens is unknown (Levy, Crown, & Reid, 2003; Seal, 2007).

Some centres have reported that higher doses of estrogens are consumed than are prescribed (Moore et al., 2003). Additional products, including phytoestrogens, may be purchased and taken. Adverse effects and interactions of these agents are largely unknown. It is likely that adverse effects of estrogens, including the cardiovascular risks, are dose-related.

**Gonadotrophin releasing hormone agonists and anti-androgen agents**

Gonadotrophin releasing hormone agonists are gonadotrophin releasing hormones analogues (e.g. goserelin or leuprorelin) that produce reversible ‘chemical gonadectomy’. By super-stimulation of the pituitary, the gonadotrophin releasing
hormone receptors on the pituitary are down-regulated and the pituitary rapidly becomes unresponsive, leading to cessation of secretion of the gonadotrophins. Luteinizing hormone (LH) and Follicle-Stimulating hormone (FSH) levels will fall to hypopituitary levels, which in turn leads to inhibition of androgen and oestrogen production in both sexes. They have growing popularity because of their desirable clinical effect in both trans women and trans men.

Antandrogens commonly used include cyproterone acetate and spironolactone. Both suppress the natural androgen’s effect in trans women by blocking androgen receptors. Side-effects of cyproterone include: fatigue, depression and, rarely, liver dysfunction (Joint Formulary Committee, 2008). Side-effects of spironolactone include: gastrointestinal upset (Joint Formulary Committee, 2008), hyperkalemia and hypotension (Dahl, 2006). Finasteride and dutasteride inhibit the conversion of testosterone to the more active dihydrotestosterone and can discourage male pattern hair loss and testosterone-dependent body hair growth. However, they have modest effect in suppressing the testosterone level clinically.

What has been recommended and why?

Oestrogen patches avoid first pass metabolism and should have less effect on liver enzymes. It is reported that transdermal oestradiol used in patients over the age of 40 reduces the occurrence of vascular events (Dahl et al., 2006; Moore et al., 2003; van Kesteren, Asscheman, Megens, & Gooren, 1997). Patches can cause minor problems such as skin irritation or poor adherence to the skin.

Futterweit (1998) gave a comprehensive description of his practice in prescribing and follow-up care, with specific advice such as contraindications for hormone treatment, which has been adopted by many other authors (Table 1). The advice given here is to withdraw oestrogen therapies for one month before surgery to reduce the risk of deep vein thrombosis (DVT). This is based on more than 20 years of clinical experience with transsexual patients.

Schlatterer, von Werder and Stalla (1996) placed emphasis on the “multi-step” treatment approach for gender dysphoria both in trans women and trans men. The first step is a psychiatric assessment followed by a “real-life test” of at least 12 months. Only after this can cross-hormone treatments begin. It should be noted, Table 1. Absolute and relative contraindications to cross sex hormone therapy in transsexual people (Futterweit, 1998).

1. Severe hypertension
2. Ischaemic heart disease and other cardiac diseases
3. Thrombophlebitis or thromboembolic disease
4. Cerebrovascular disease
5. Hepatic dysfunction
6. Renal impairment
7. Refractory migraine, seizures, or retinal lesions
8. Brittle or poorly controlled diabetes
9. Hyperprolactinaemia
10. Strong family history of breast cancer
11. Heavy cigarette consumption
12. Marked obesity
13. Hypertriglyceridaemia or hypercholesterolemia in genetic females
however, that since the 1990s the emphasis on real life experience prior to hormone therapy has relaxed in the field.

Michel, Mormont and Legros (2001) suggested three stages of hormonal therapy required for both trans women and trans men: (1) presurgical, suppression of the ongoing sexual characteristics (optional); (2) presurgical, induction of desired sexual characteristics; and (3) post-surgical. Included is a review of the psychological aspects and differential diagnosis of gender identity disorder.

Tangpricha, Ducharme, Barber and Chipkin (2003) recommended initiating oestrogens at low doses with increases every two to three months. Blood hormones levels are then measured every three months. Patients with persistently high serum testosterone levels may benefit from spironolactone. After two years of oestrogen therapy, patients should be monitored for complications at least semi-annually.

Toorians, Thomassen, Zweegman, Magdeleyns, Tans, et al. (2003) studied the change of haemostatic variables during cross-sex hormone treatment. They conclude that treatment with cyproterone acetate (CPA) only, CPA plus transdermal 17-beta-estradiol (E2) and CPA plus oral E2 (valerate) produced small effects on haemostatic variables, whereas oral ethinyl estradiol (EE) treatment resulted in a large increase in haemostatic variables, which are known risk factors for venous thrombosis.

Moore et al. (2003) published guidelines for hormone treatment and a protocol for investigations and follow-up. They recommend the use of EE or conjugated oestrogen orally. Transdermal patch is recommended once the patient is over 40 years old. The aim is to adjust dosage to suppress total testosterone to less than 25 ng/dl. If high dose oestrogen fails to suppress the total testosterone level adequately, it is necessary to add spironolactone, cyproterone or GnRH agonists to reduce overall oestrogen dose requirements. The addition of progesterone should be considered with caution because of possible increased risk of thrombotic illness with combined oestrogen and progesterone. With regard to monitoring, initial blood screen includes prostate specific antigen (PSA), lipid profile and liver function tests. Pre-op monitoring includes testosterone levels until stable in the mid-range of biological-age-related serum levels; estradiol blood level to assess compliance; liver function, lipid profile, prolactin and a breast examination. The above should be monitored every 3–6 months in the pre-operative phase. Mammogram can be considered if the patient is over 50 years old; prolactin levels and visual field tests should be performed to assess for prolactinoma; PSA should be checked every 6–12 months if the patient is over 50 years old (to screen for prostate cancer). For post-operative patients, oestrogens should be reduced to hormone replacement therapy doses. A Dexa scan should be considered to assess for osteoporosis.

Levy et al. (2003) recommended oestradiol patches releasing 100ug/day, EE 50ug three times a day orally or oestradiol valerate (the pharmacological equivalent of natural 17-beta-oestradiol) 2mg three times a day for pre-operative patients. For post-operative patients, recommendations are Estradiol patches releasing 50ug/day, EE 50ug daily orally or oestradiol valerate 2mg daily. Anti androgens are suggested for augmentation of feminizing effects of oestrogen in both pre-op and post-operative patients, in the form of cyproterone acetate, flutamide or spironolactone. Progestogens are believed to augment the oestrogen-induced breast development and to exert useful psychological effects, such as maintenance of libido. The authors recommended a flexible protocol to incorporate individuals who do not proceed to sex reassignment surgery or who want to step in and out of medical treatment to suit their needs. Apart from psychiatric assessment, baseline screening should include a
physical examination with a sensitive approach; cholesterol, urea and electrolytes, glucose, liver function tests and sex hormone levels should be obtained. Bone mineral density is protected by oestrogens from osteopenia and osteoporosis. After confirmation of diagnosis, it is necessary to receive formal consent before starting treatments. These recommendations are based on literature reviews and the personal experience of Dr. Russell Reid who has managed over 3000 transsexual patients in the UK.

In 2004, T'sjoen, Rubens, De Sutter and Gooren responded to the review by Moore et al. (2003). T'sjoen advised a slow titration rather than a quick transition into hormones because of psychosocial adjustment and the irreversible nature of cross-sex hormone treatment. The first reversible phase includes antiandrogens, which are used as part of the real life experience. This is to be followed by administration of cross-sex hormones, with largely irreversible feminization. This regime may have the advantage of allowing a lower dosage of oestrogen and hence reducing the risk of side-effects and morbidity. Nevertheless, the role of oestrogen remains the most important component for facilitating full transition (Dobs & Moore, 2004).

Gooren (2005) emphasized the importance of counselling to avoid unrealistic expectations from patients. With regard to hormone preparations, Gooren recommended dual therapy of combined antiandrogen and oestrogen. Antiandrogen can be chosen from one of the following selections: most widely used cyproterone acetate, medoxyprogesterone acetate, non-steroidal antiandrogens (Flutamide/Nilutamide), spironolactone, gonadotropin releasing hormone agonist, or finasteride. As for the use of oestrogens, oral 17beta-oestradiol valerate or transdermal 17beta-oestradiol is the preferred treatment at Gooren's Amsterdam clinic over the use of EE, which carries risk of venous thrombosis. Injectable oestrogens are used less frequently because of higher risk of overdose. Gooren also raised the issue of juvenile gender dysphoria, which is coming increasingly to the attention of the healthcare professionals. Under expert opinion, those individuals can delay their pubertal sexual maturation by hormone preparations.

Dittrich, Binder, Cupisti, Hoffman, Beckmann, et al. (2005) recommended the use of GnRH analogues by monthly injection and oestradiol-17beta valerate. These recommendations are based on results of a sample of 60 people, all of whom experienced a decline in gonadotrophins, total testosterone and free testosterone and an increase in oestradiol and SHBG serum levels. This had the desirable clinical effects of increase in breast size, as well as an increase in bone mass density. The treatment regimen was well tolerated with very few side-effects.

A cross-sectional study by Ruetsche, Kneubuehl, Birkhaeuser, Lippuner, et al. (2005) in Switzerland explored the effect of long-term cross-sex hormonal treatment on bone mineral density (BMD) in 39 transsexuals. In trans women, BMD was preserved over a median of 12.5 years of anti androgen and oestrogen combination therapy, whilst in trans men BMD was either preserved or increased to normal male levels after a median of 7.6 years of androgen treatment.

Dahl et al. (2006) recommended a feminising regimen and protocol for laboratory investigations. The recommended regimen for trans women is a combination of oestrogen and spironolactone. Transdermal oestradiol is preferred if the patient is over the age of 40 or is at increased risk of DVT. The dose starts at 0.1 mg/24 hours, applied twice per week and can be increased up to maximum of 0.2 mg/24 hours, applied twice per week. Alternatively, oral 17beta estradiol can be started at 1–2 mg daily and
gradually increased to a maximum of 4mg daily. The risk of adverse effects from taking spironolactone, such as hyperkalemia, can be exacerbated by taking ACE-inhibitors. Finasteride may be added to slow male pattern balding, at a dose of 2.5–5 mg daily. The dose of oestrogen should be reduced after orchidectomy. Alternative forms of taking oestrogen include intramuscular (IM) injections and oestradiol gel.

Based on experience with approximately 2500 patients at the Charing Cross clinic in London, Seal (2007) reviewed organic disorders and hormonal disorders that may present with gender dysphoria. He recommended a full screening of sex hormone profiles during the initial visits. He concluded that hormonal manipulation of patients with gender dysphoria does not alter their standard mortality ratio, confirming that these treatments are safe as well as effective (Seal, 2007, pp. 185–186). The major side-effect of oestrogen therapy for trans women is thromboembolism, usually as DVT with a rate of 2–3% in Seal’s clinic population. Other important risks include breast cancer, liver enzyme derangement and hyperprolactinaemia. The management of the above complications are well described. Regarding the beneficial effects, breast development plateaus after two years of hormone therapy and no evidence was found that progestins improve breast development. The standard hormone regimen used is the initiation of oestrogen valerate 2 mg increasing to a maximum of 6mg/day, titrated according to serum oestradiol level aiming for 400–600pmol/l. The dose is titrated every three months. Goserelin 10.8mg/12 weeks is added to suppress testosterone production. To cover the flare in testosterone levels for the first two weeks after goserelin injection, cyproterone acetate 100 mg daily is an optional addition. Goserelin can be given at higher frequency of once every 10 or 11 weeks (rather than 12 weeks) until plasma testosterone falls to the normal female range (<3 nmol/l). In older patients, oestrogen monotherapy may be adequate to achieve testosterone suppression. Other alternative preparations of oestrogen being used include transdermal oestrogen 50–100microgram twice per week or EE 50–150 microgram daily. For the treatment of male pattern hair loss, Seal recommended cyproterone, spironolactone or finasteride as well as goserelin injection.

**Our recommendations**

We appreciate that there has been reluctance by many practitioners to use GnRH agonists, which have the potential to completely suppress normal testicular or ovarian secretion of sex steroids. Sexual function (such as morning erections for trans women) and menstruation in trans men will cease, usually with great relief to the individual. Whilst GnRH agonists are more expensive and require subcutaneous injections every 4 or 12 weeks (depending on the dosing), they are most effective in lowering the base sex steroid level and they are very well tolerated with very few side-effects, especially if co-administered with another sex steroid (oestradiol in trans women and testosterone in trans men). The potentially unpleasant and detrimental side-effects of agents such as cyproterone or spironolactone can be avoided. The absence of endogenous sex steroids has the benefit of lower requirements of cross-sex hormone doses with reduced likelihood of untoward side-effects, especially thrombosis from higher doses of estrogen therapy.

Before commencing treatment, a full physical examination should be offered and recorded in the notes (Table 2). The option of storage of gametes should be discussed with patients. Genital exam may cause individual distress and may be declined by the patient; such refusals should be documented and respected in all cases (Vardi et al., 2008). Breast cancer awareness information should be offered. Patients should be
encouraged to stop smoking, exercise regularly, have a sensible diet and consume no more than 14 units of alcohol per week. Most importantly, patients must give informed consent before starting treatment and be fully aware of all expected and adverse effects (Department of Health, 2007). Monitoring of expected and any adverse effects should occur as indicated in Table 3.

Table 2. Recommendations for hormone therapy for trans women.

| To suppress androgen secretion and action | Either goserelin 3.6 mg subcutaneously, four weekly or 10.8 mg implanted twelve weekly, or equivalent. Or, one of the following agents: 1. Cyproterone 50–100 mg daily 2. Spironolactone 100–400 mg daily 3. Finasteride 5 mg daily, particularly to treat male pattern hair loss Note: Goserelin can be used in addition to the above 3 anti-androgens as they differ in mechanism of action. Progesterone is not indicated since no biologically significant receptor sites exist for biological males. |
| To bring about feminisation of the male body | Oral Estradiol 1–6 mg daily or estradiol patches (50 mcg–150 mcg, 2–3 times per week), particularly for patients over 40 years of age (lower risk of thrombosis). Dosage of estrogen depends on results of circulating estradiol level – see Table 3. |

Table 3. Physical monitoring for trans women.

| Baseline measures | Blood pressure, full blood count, urea and electrolytes, liver function tests, fasting glucose, lipid profile, thyroid function, testosterone, estradiol (<100 pmol/l), prolactin (50–400 mU/L) |
| Monitoring | On a six-monthly basis for three years and then yearly, depending on clinical assessment and results. Provision of prescription is contingent on satisfactory tests, namely: blood pressure, full blood count, urea and electrolytes, liver function test, fasting glucose, lipid profile, testosterone, serum estradiol 24 hours after a tablet or 48 hours after application of a patch (levels should be in the upper half of the normal follicular range, 300–400 pmol/L), prolactin (<400 mU/L) |
| Surgery and post-operatively | Stop hormones four weeks before surgery and cover with a single dose of goserelin 3.6 mg stat dose. Hair growth can occur when the effects of goserelin wear off after four weeks. Hormones, namely estradiol tablets or patches for those age 40 or older, should be resumed four weeks post-op if there are no complications. Anti-androgens are usually not required but androgens may still be significantly derived from adrenals; finasteride as above can be prescribed if androgen effects are still evident. Monitoring for osteoporosis, breast cancer and prostate cancer is required. Oestrogen, usually at a lower dose, and tests needed for life as described above on a six-monthly basis for three years, then yearly if stable. |
Trans men

The basis of treatment

Overall, in the biological male, androgens are responsible for development of internal and external genitalia during fetal development and establishment and maintenance of secondary sexual characteristics (Greenspan & Gardner, 2004). They also stimulate erythropoiesis and social behavioural changes in the adolescent male.

In trans men, treatments are testosterone induction, usually by injection, and leuprolelin acetate (a GnRH agonist) if required to cease the menstrual periods. Usual outcomes include suppression of menstruation, redistribution of body fat, clitoral enlargement, deepening of the voice, which is irreversible (Gooren, 2005), and thickening and increasing of body hair as well as changing its distribution. Reversible changes include increased upper body strength, weight gain, increased social and sexual interest and arousability and decreased hip fat. Nevertheless, breasts size will not substantially shrink with testosterone (Dahl et al., 2006).

Side-effects include: polycythaemia and increased haematocrit; liver dysfunction; emotional instability, aggression and excessive sex drive; endometrial hyperplasia (reported risk of 15%: Futterweit, 1998); acne; infertility; change of lipid profiles increasing cardiovascular risks, decreased insulin sensitivity and increased blood pressure; male pattern alopecia; headache/migraine; and exacerbation of obstructive sleep apnea (Futterweit, 1998; Seal, 2007). Two cases of ovarian cancer have been reported (Hage, Dekker, Karim, Verheijen, Bloemena, 2000).

What has been recommended and why?

Futterweit (1998) followed the course of treatment in 92 female to male transsexuals over 22 years. It should be noted that, without exception, all of the participants went on to sex reassignment surgery after psychiatric assessment, compared to only 40–50% of trans women. Almost one-third of the patients had menstrual dysfunction and significant hirsutism before testosterone therapy and there was a 25% incidence of polycystic ovary syndrome. Treatment consisted of testosterone ester injections (enanthate or cypionate) 250–400 mg IM every 2–3 weeks. Cessation of menses typically occurred after one or two injections.

Schlatterer et al. (1996) emphasized the importance of a “multi-step” treatment for both trans women (see above) and trans men. Trans men require IM testosterone injections, usually starting with a dose of 250 mg every two weeks. When secondary sex characteristics are satisfactory for the patient, usually after 9–12 months, testosterone doses are reduced according to serum hormone levels to an injection approximately every three weeks. The most common side-effect was acne.

Tangpricha et al. (2003) recommended bimonthly IM injections of testosterone esters. In Europe, a safe oral preparation of 17β- alkylated testosterone is available, but elsewhere, other oral agents may cause hepatotoxicity. Recommended starting doses for injections are between 50 and 80 mg every two weeks, increasing monthly until menstruation stops, which is usually within two or three months. After cessation of menses, required doses are often between 100 mg and 200 mg fortnightly.

Levy et al. (2003) described Sustanon 250 mg IM or testosterone enanthate (Primoteston Depot) 100 mg IM every two weeks as the usual treatment for trans men. Based on a review of the literature, Levy concluded that the effect of hormones on the bones for trans men is equivocal. Levy noted that there are very few well validated efficacy data for different treatments relevant to trans men.
Moore et al. (2003) found that testosterone injections were the most regularly used preparations in the USA, before and after oophorectomy. Outside the USA, oral testosterone undecanoate can maintain adequate serum testosterone although may need the addition of a progestin to fully suppress menstruation. Transdermal applications may correspond more closely with physiological testosterone than other preparations.

T'Sjoen et al. (2004) commented on the paper by Moore et al. (2003). As stated above for trans women, T'Sjoen advocated a slow transition phase for trans men of typically two years in duration. He recommended that trans men start on progestins (e.g. lynestrenol 5mg) before progressing further to testosterone. He also suggested routine karyotyping to diagnose intersex conditions as part of the baseline physical assessment.

Gooren (2005) recommended testosterone esters in doses of 200 to 250 mg by IM injection every two weeks. He mentioned the future use of testosterone undecanoate 1000 mg injections only needed every 10–12 weeks. Gooren also suggested the addition of a progestational agent if menses do not cease, which is almost always needed if transdermal or oral testosterone preparations are used.

Seal (2007), based on experience at the Charing Cross Gender Identity Clinic, recommended the use of testosterone enanthate esters IM injection 2–4 times weekly resulting in masculinisation over 2–4 years. Doses of 250 mg usually suffice to suppress menstruation. The frequency and dose of injection should be titrated according to testosterone levels in blood. Menses usually stop after one or two injections of testosterone. Oral testosterone results in lower androgen levels than injectable testosterone. The former may fail to suppress menses without the addition of a progestin. In these cases, medroxyprogesterone acetate 10 mg three times daily or Norethisterone 15–25mg/day can be used to suppress menstruation. According to Seal, the major side-effects of testosterone in trans men are polycythaemia and the development of endometrial hyperplasia due to aromatisation of testosterone to estradiol. Polycythaemia can be treated with dose reduction or venesection. Endometrial hyperplasia can be screened for with serial ultrasound scanning until after hysterectomy. More minor side-effects include increased triglyceride level, abnormal liver function tests and possible osteoporosis.

Finally, Dahl et al. (2006) recommended IM or transdermal testosterone preparations as they minimise hepatic exposure and, hence, reduce potential adverse hepatic effects. Dosage of IM esterified testosterone should begin with 25–40mg/week or 50–80mg/fortnight, increasing monthly according to blood testosterone levels to the usual maintenance dose of 50–100mg/week or 100–200mg/fortnight. Transdermal gel or patch may be used if preferred by patients, but they are much more expensive. Oral testosterone is generally less effective than IM/transdermal preparations. Progestins or GnRH analogues can be used to assist with menstrual cessation, although they are not commonly used due to the cost and side-effects. After two years of treatment or after oophorectomy, doses of testosterone can be reduced to keep serum testosterone within the lower-middle range end of the male reference interval. Calcium and vitamin D should be supplemented after oophorectomy to help preserve bone density.

**Our recommendations**

To suppress oestrogen secretion and action, the use of long acting GnRH analogue, such as goserelrin or leuprorelin, will rapidly but reversibly suppress LH, FSH and
ovarian function. To bring about masculisation of the female body, testosterone therapy can be commenced. It is usual to use depot injection of testosterone enanthate 250–500 mg IM 2–6 weekly depending on serum testosterone levels (see Table 4). The new long-acting testosterone 1000 mg can be used with success to space out the interval of injection (10–12 weekly). Alternatively, testosterone gel may be used (50 mg/5 g gel once daily, occasionally two doses are required). Transdermal patches are frequently poorly tolerated. Oral testosterone undecanoate (120–160 mg/day in separate doses) is another option, in which case monitoring of the dosage should be based on circulating dihydrotestosterone (DHT) levels in blood obtained 3–4 hours after a dose because of its unique pharmacokinetics.

Before commencing hormone therapy, a full physical examination should be completed (Verdi et al., 2008). Genital examination is not necessary if pelvic ultrasound is performed. Similarly to trans women, trans men should be encouraged to stop smoking, exercise regularly, have a sensible diet and consume no more than 14 units of alcohol/week. The option of storage of gametes should be discussed. Informed consent should be obtained (Department of Health, 2007). Monitoring of expected and any adverse effects should occur, as indicated in Table 4.

### Table 4. Physical monitoring for trans men.

| Baseline measures | Blood pressure, FBC, urea and electrolytes, LFT, fasting glucose, lipids, thyroid function, prolactin (<400 μu/l), estradiol and testosterone |
| Monitoring | Six-monthly for three years and then yearly if well: blood pressure, FBC, urea and electrolytes, LFT, fasting glucose, lipids, estradiol (should be in the male range), prolactin. Testosterone should be at or below lower end of normal range (<12 nmol/L) just below next dose is due to avoid accumulation or inadequate dosage. If on oral testosterone, measure DHT level 3–4 hours after a dose |
| Surgery and post-operatively | Hormones do not need to be stopped pre-operatively. Testosterone should be continued for life if there are no contraindications. Monitoring for osteoporosis and breast cancer is required. |

Notes: FBC = full blood count; LFT = liver function tests; DHT = dihydrotestosterone.

Conclusion

A number of authors have described their clinical experience and recommendations for prescription of cross-sex hormones; these recommendations have been described in detail. Clinical experience with gender dysphoric patients and cross-sex hormones has led to the development of these recommendations. Based on this review and our own clinical experience, we recommend prescription of a GnRH agent as a first treatment for both trans women and trans men. The advantage is a reduced need for replacement sex steroids with lower likelihood of side-effects from both agents used to reduce endogenous sex steroids and from replacement sex steroid doses. The expectation of improved quality of life and lower risk of side-effects justifies the higher cost of prescribing a GnRH for the duration of the real life experience. For trans women, we advise the use of transdermal estrogen and a GnRH agonist pre-surgery. For trans men, we advise the use of testosterone gel or injection and a GnRH agonist pre-surgery. Adequate monitoring of the haematological,
biochemical and physical consequences of these preparations is essential. Appropriate sex steroids should be continued post-surgery for life with regularly monitoring.

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References


